DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

February 2015

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 11 and 12, 2015, at the Defense Health Agency (DHA) Formulary Management Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of November Minutes**—Lt. Gen. Douglas J. Robb, DO, MPH, Director, DHA, approved the minutes from the November 2014 DoD P&T Committee meeting on February 3, 2015.

2. **Correction to the November 2014 Minutes**

   a) Self-Monitoring Blood Glucose Test Strips—The November minutes were corrected to state the implementation period for the self-monitoring blood glucose test strips will be 180 days, instead of 120 days. The implementation date is August 5, 2015.

   b) Compound Prescriptions—The Director's decision is final regarding the manual prior authorization (PA) criteria for all new and current users of compound prescriptions. Coverage will be approved if the prescriber provides the information listed in the March 11, 2015 signed Determination Letter on Compounds and implementation of the PA will occur no later than May 1, 2015.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Newer Sedative Hypnotics Agents (SED-1s): Tasimelteon (Hetlioz)

Background—Tasimelteon (Hetlioz) is a melatonin receptor agonist indicated solely for treatment of the non-24 sleep wake disorder, a circadian rhythm disorder sometimes found in blind patients.

Only two placebo-controlled trials in patients with non-24 sleep wake disorder are available; no head-to-head or active comparator studies are available. Many limitations exist with these two studies, including the small numbers of patients enrolled (less than 100 patients), the inclusion of patients shown to previously respond to tasimelteon (RESET trial), and the high patient discontinuation rate (SET trial).

One study in sighted patients with insomnia showed improvements in sleep parameters, but other products on the UF [e.g., zolpidem, eszopiclone (Lunesta)] should be prescribed for insomnia instead of tasimelteon.

Two agents with a similar structure as tasimelteon [melatonin supplement and ramelteon (Rozerem)] are marketed to treat insomnia caused by difficulties with sleep onset.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that other than its unique indication for treating blind patients with non-24 sleep wake disorder, tasimelteon offers no clinically compelling advantages over the existing SED-1 drugs on the UF that are used to treat sleep disorders.

Relative Cost-Effectiveness Analysis and Conclusion—Cost-minimization analysis (CMA) was performed. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) tasimelteon (Hetlioz) is more costly than the formulary and nonformulary SED-1 agents and melatonin.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) tasimelteon (Hetlioz) be designated NF due to the lack of compelling clinical advantages, other than its unique indication, and cost disadvantage compared to SED-1 agents on the UF.
2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for tasimelteon (Hetlioz). See Appendix B for the full criteria.
3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** Automated (step therapy) and manual PA criteria were recommended at the August 2014 DoD P&T Committee meeting and implemented December 10, 2014 for tasimelteon, requiring a trial of zolpidem immediate release (IR) or zaleplon first, and a diagnosis of blindness. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) updating the PA criteria for tasimelteon, including removing the step therapy requirement, and requiring all new patients to undergo the manual PA process. See Appendix C for the full criteria.
4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent)

1) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS); and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is July 15, 2015.

5. ***COMMITTEE ACTION: EXCLUDE FROM 2015 NDAA SECTION 702 REQUIREMENT FOR NF MEDICATIONS AVAILABLE AT MAIL ORDER ONLY***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) tasimelteon be excluded from the requirement that NF drugs be solely available from the ~~TRICARE~~ Mail Order Pharmacy. See Section VIII.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors: Empagliflozin (Jardiance)

Background—Empagliflozin (Jardiance) is the third FDA-approved SGLT2 inhibitor. The drug is effective in lowering hemoglobin A1c (A1c) by about 0.65%–0.8% when used as monotherapy, by about 0.5%–0.8% as part of dual therapy, and by about 0.6%–1.3% as part of triple or quadruple therapy. It is similar to canagliflozin (Invokana) and dapagliflozin (Farxiga) in terms of its effects on increasing low-density lipoprotein cholesterol, increasing high-density lipoprotein cholesterol, and decreasing systolic blood pressure and body weight.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) empagliflozin offers no clinically compelling advantages over the existing UF non-insulin diabetes drugs, given the modest decrease in A1c, risk of adverse reactions, including female genital mycotic infections and urinary tract infections, and unknown long-term cardiovascular safety profile.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate empagliflozin (Jardiance) with other oral products on the UF used in the treatment of diabetes. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) the following:

- CMA results showed empagliflozin (Jardiance) was not cost effective compared to existing formulary agents in the non-insulin diabetes class including metformin, sulfonylureas, thiazolidinediones, and dipeptidyl-dipeptidase-4 (DPP-4) inhibitors.
- Current costs for empagliflozin (Jardiance) show it was comparable to canagliflozin (Invokana) and dapagliflozin (Farxiga), the other agents available in the SGLT2 subclass.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent)

empagliflozin (Jardiance) be designated NF due to the lack of compelling clinical advantages, safety concerns, lack of long-term outcomes, and cost disadvantage compared to the oral UF products used for treating diabetes.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for empagliflozin (Jardiance). See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) a trial of metformin or a sulfonylurea and a DPP-4 inhibitor in all new and current users of empagliflozin (Jardiance), consistent with the PA requirements in place for canagliflozin and dapagliflozin. See Appendix C for full criteria.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD*** The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, DHA, Decision ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Antiplatelet Agents: Vorapaxar (Zontivity)

Background—Vorapaxar (Zontivity) is a new antiplatelet with a novel mechanism of action [protease-activated receptor-1 antagonist] that inhibits thrombin-induced platelet activation. It is approved in the setting of secondary prevention for the reduction of cardiovascular (CV) events (including CV death, myocardial infarction (MI), and stroke) in patients with a history of MI or with peripheral artery disease. Vorapaxar must be used with aspirin and or clopidogrel. It remains unknown whether adding vorapaxar to aspirin and or clopidogrel offers benefits similar to that seen with other antiplatelet agents.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that clinically, the place in therapy for vorapaxar is limited due to the significantly increased bleeding risk. Vorapaxar should be reserved for those patients with stable atherosclerotic disease who have failed other antiplatelet therapies.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate vorapaxar (Zontivity) with other oral antiplatelet agents on the UF. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that vorapaxar (Zontivity) was not cost effective compared to other oral antiplatelet agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) vorapaxar (Zontivity) be designated NF based on clinical and cost effectiveness.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) MN criteria for vorapaxar (Zontivity). See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. Phosphodiesterase-5 (PDE-5) Inhibitors for Erectile Dysfunction (ED): Avanafil (Stendra)

Background—Avanafil (Stendra) is the fourth PDE-5 inhibitor for ED to enter the market. There are no head-to-head clinical trials comparing avanafil with the other PDE-5 inhibitors for treating ED. However, the change in efficacy endpoints for ED with avanafil and the safety profile appears similar to the other PDE-5 inhibitors. In one study, the higher doses of avanafil were effective in improving ED after prostatectomy, compared to placebo.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that although avanafil differs from the other PDE-5 inhibitors in that it has a 15-minute onset of action, only one PDE-5 is required on the UF to meet the needs of the Military Health System (MHS).

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) avanafil (Stendra) was more costly than the other UF and NF PDE-5 inhibitors.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) avanafil (Stendra) be designated NF due to the lack of compelling clinical advantages and the cost disadvantage compared to the BCF, step-preferred product, sildenafil (Viagra).

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for avanafil (Stendra). See Appendix B for the full criteria.

3. ***COMMTTEE ACTION: PA CRITERIA***—Existing automated (step therapy) PA criteria for the PDE-5 inhibitors used for the treatment of ED requires a trial of sildenafil (Viagra) first, prior to receiving another PDE-5 inhibitor. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) PA criteria for all current users of avanafil (Stendra), similar to the existing PA criteria for the class. See Appendix C for the full criteria.

4. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) QLs for avanafil (Stendra), consistent with the FDA-approved package labeling and the QLs in place for the other PDE-5s used in for the treatment of ED. See Appendix E for QLs.

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) an 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, DHA, Decision: ☐ Approved ☐ Disapproved

Approved, but modified as follows:

E. Proton Pump Inhibitors (PPIs): Esomeprazole Strontium

Background—Esomeprazole strontium (no brand name) is the eighth PPI to reach the market. It was approved via section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using efficacy and safety data primarily obtained from information contained in the package insert for esomeprazole magnesium (Nexium).

There are no clinical trials assessing efficacy. Esomeprazole strontium has the same indications as Nexium, with the exception that it is not approved for children. The FDA concluded that that daily dose of strontium contained in the product is not a significant risk to bone health.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that esomeprazole strontium offers no clinically compelling advantages compared to esomeprazole magnesium (Nexium) or the other PPIs.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that esomeprazole strontium is not cost effective compared to other PPIs on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) esomeprazole strontium be designated NF due to the lack of compelling clinical advantages and the cost disadvantage compared to the other PPIs on the UF.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for esomeprazole strontium. See Appendix B for the full criteria.

3. ***COMMTTEE ACTION: PA CRITERIA***—Existing automated (step therapy) PA criteria for the PPIs requires a trial of Nexium or omeprazole first, prior to receiving another PPI. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) PA criteria for all new and current users of esomeprazole strontium similar to the existing PA criteria for the class. See Appendix C for the full criteria.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) an 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, ~~DHA~~, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Pulmonary Arterial Hypertension (PAH) Agents

Background—The P&T Committee reviewed the clinical effectiveness of the PAH Agents, which is divided into the three subclasses outlined below. The intravenous prostacyclins (e.g., Flolan and Remodulin) and PDE-5 inhibitors indicated for ED (e.g., Viagra, Cialis, and Levitra) were not included in the review.

- **Prostacyclins**: treprostinil nebulized solution (Tyvaso), treprostinil oral tablets [Orenitram extended release (ER)], and iloprost nebulized solution (Ventavis);

- **Endothelin Receptor Antagonists (ERAs)**: bosentan (Tracleer), ambrisentan (Letairis), and macitentan (Opsumit);
- **Nitric Oxide Drugs**: the soluble guanylate cyclase stimulator, riociguat (Adempas); and, the PDE-5 inhibitors, sildenafil generic, sildenafil brand (Revatio), and tadalafil (Adcirca).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) the following for the PAH agents:

1. There are no head-to-head comparisons among the PAH drugs; therefore, no evidence-based first-line treatment can be proposed.
2. For the PDE-5 inhibitors, there was no new data to change the conclusion from the previous UF review (November 2009).
    - Sildenafil and tadalafil show similar improvements in 6-minute walking distance (6MWD), based on indirect comparisons of clinical trial results.
    - The product labeling for the two drugs is similar with regard to contraindications, precautions, and warnings.
    - Tadalafil (Adcirca) is dosed once daily, which is more convenient compared to the three-times daily dosing required with sildenafil (Revatio).
3. In one systematic review (CHEST 2014), all the PAH drugs increased the 6MWD by 27.9 meters to 39.9 meters when compared to placebo; however, comparisons between agents are inconclusive. Of note, the minimal clinically important difference for the 6MWD is a distance of at least 33 meters.
4. Monotherapy with the ERAs or PDE-5-inhibitors showed decreased hospitalization rates. There is insufficient information to determine whether ERAs or the PDE-5 inhibitors decrease mortality.
5. The CHEST 2014 systematic review did not include treprostinil (Orenitram ER), macitentan (Opsumit) and riociguat (Adempas). In their individual trials, Orenitram ER, Opsumit, and Adempas caused statistically significant improvements in the 6MWD compared to placebo. The improvement in 6MWD was clinically significant with Adempas. Orenitram ER and Adempas have not shown mortality benefits. Orenitram ER showed a significant reduction in the endpoint of time to clinical worsening. Adempas has an additional indication for chronic thromboembolic pulmonary hypertension (CTEPH).
6. Within and among the subclasses, the PAH drugs have distinct adverse reaction profiles. The ERAs and riociguat are pregnancy category X.

Overall relative clinical effectiveness conclusion: The P&T Committee concluded the choice of drug for PAH depends on a variety of factors including indication, product labeling, mechanism of action, route of administration, side effect profile, drug interactions, patient preference, and physician experience.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and budget impact analysis (BIA) was performed to evaluate the PAH subclasses. BIA was performed to evaluate

the potential impact of designating selected agents in various formulary scenarios. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) the following:

ERAs:

- CMA results showed that ambrisentan (Letairis) was the most cost-effective agent in this subclass, followed by macitentan (Opsumit) and bosentan (Tracleer).
- BIA results showed that the scenario with Letairis, Opsumit, and Tracleer designated with UF status and no step requirement yielded the lowest budget impact for the MHS.

Prostacyclins:

- CMA results showed that treprostinil tablets (Orenitram ER) was the most cost-effective agent in this subclass, followed by treprostinil nebulized solution (Tyvaso) and iloprost (Ventavis).
- BIA results showed that the scenario with Orenitram ER, Tyvaso, and Ventavis designated with UF status and no step requirement yielded the lowest budget impact for the MHS.

Nitric Oxide Drugs:

- CMA results showed that sildenafil generic was the most cost-effective agent in this subclass, followed by tadalafil (Adcirca), sildenafil brand (Revatio), and riociguat (Adempas).
- BIA results showed that the scenario with sildenafil generic and sildenafil brand (Revatio) as step-preferred and formulary on the UF, with tadalafil (Adcirca) and riociguat (Adempas) as non step-preferred and formulary on the UF, yielded the lowest budget impact for the MHS.

a) ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) the following:

- ERAs: designate bosentan (Tracleer), ambrisentan (Letairis), and macitentan (Opsumit) as UF.
- Prostacyclins: designate treprostinil nebulized solution (Tyvaso), treprostinil tablets (Orenitram ER), and iloprost (Ventavis) as UF.
- Nitric Oxide Drugs:
    - UF and step-preferred: sildenafil 20mg generic and sildenafil brand (Revatio)
    - UF and non step-preferred: tadalafil (Adcirca) and riociguat (Adempas)

- This recommendation includes step therapy, which requires a trial of sildenafil 20 mg generic or sildenafil brand (Revatio) in all new users of tadalafil (Adcirca) or riociguat (Adempas).

b) ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) adding sildenafil 20mg generic and sildenafil brand (Revatio) tabs to the ECF.

c) ***COMMITTEE ACTION: NITRIC OXIDE DRUGS PA CRITERIA*** Existing manual PA criteria apply to sildenafil 20 mg (Revatio) or tadalafil (Adcirca) for patients with primary PAH. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) automated (step therapy) criteria for all new users of the non-preferred nitric oxide PAH drugs [tadalafil (Adcirca) and riociguat (Adempas)], requiring a trial of sildenafil 20 mg generic or sildenafil brand (Revatio) first. See Appendix C for the full criteria.

d) ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Oral Oncology Drugs—Prostate Cancer

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Prostate Cancer drugs, which is comprised of the following:

- **Subclass I (Anti-Androgen Agents)**: bicalutamide (Casodex; generic), flutamide (Eulexin; generic), and nilutamide (Nilandron)

- **Subclass II (Survival-Prolonging Drugs)**: enzalutamide (Xtandi) and abiraterone (Zytiga)

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for the Prostate Cancer drugs:

- **Subclass I (Anti-Androgen Agents):**
    1. The American Society of Clinical Oncologists/Cancer Care Ontario 2014 Guidelines found only limited data regarding clinical benefits of the Subclass I agents (bicalutamide, flutamide, and nilutamide). The guidelines also stated that the three anti-androgens demonstrate unknown survival and quality of life benefit.
    2. In one head-to-head trial, bicalutamide was as effective as flutamide. There was no significant difference between the two drugs in the median time to progression of disease or median time to death.
    3. Flutamide has a higher incidence of gastrointestinal side effects than bicalutamide, and has warnings for hepatotoxicity. Nilutamide has a black box warning for pulmonary toxicity and delays visual light-to-dark adaptation that can limit its use.
    4. Bicalutamide is considered the initial drug of choice when used for complete androgen blockage, based on its dosing frequency (once daily dosing, compared to three times daily dosing with flutamide), toxicity profile, and clinical trial data.
    5. Although nilutamide has no compelling advantages compared with flutamide or bicalutamide and has the least favorable safety profile, it is required on the UF due to its unique indication for use in combination with surgical castration.

- **Subclass II (Survival Prolonging Drugs):**
    1. For the Subclass II agents, abiraterone (Zytiga) and enzalutamide (Xtandi) have independently been shown to improve overall survival and progression-free survival when compared to placebo, both in the post-chemotherapy and chemotherapy-naïve settings. There is no data to guide sequencing.
    2. Zytiga requires the co-administration of prednisone to help mitigate the mineralocorticoid excess that can result from its mechanism of action. Xtandi does not require concomitant administration of steroids, but 30%–47% of patients were receiving some form of steroids therapy in the two phase 3 studies that led to its FDA approval.
    3. The Subclass II agents have differing safety profiles. Zytiga can cause adrenocortical insufficiency, hypertension, hypokalemia, and edema, which requires close monitoring for these complications. Xtandi has been associated with seizures as well as hypertension when compared to placebo.

Overall relative clinical effectiveness conclusion: The P&T Committee concluded the choice of prostate cancer agent depends on clinical considerations, patient preferences, prior treatment, presence or absence of visceral disease, patient symptoms, and drug side effect profiles.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed to evaluate the Prostate Cancer drugs. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) the following:

- CMA results showed that in Subclass I, bicalutamide was the most cost-effective agent, followed by flutamide and nilutamide. In Subclass II, abiraterone (Zytiga) was more cost effective than enzalutamide (Xtandi).
- BIA results showed that designating all the prostate cancer drugs as formulary on the UF, with no step-preferred agents in either subclass, demonstrated significant cost avoidance for the MHS.

a) ***COMMITTEE ACTION: UF RECOMMENDATIONS***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) the following:

- UF:
  - Flutamide (Eulexin; generic)
  - Bicalutamide (Casodex; generic)
  - Nilutamide (Nilandron)
  - Abiraterone (Zytiga)
  - Enzalutamide (Xtandi)
- NF: None

b) ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) bicalutamide (Casodex) be designated with BCF status.

c) ***COMMITTEE ACTION: MANUAL PA CRITERIA***—Manual PA criteria currently apply to enzalutamide (Xtandi) and abiraterone (Zytiga). The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) maintaining the current PA criteria for Xtandi and Zytiga. The P&T Committee also recommended manual PA criteria for all new users of nilutamide (Nilandron) due to its limited indication. See Appendix C for full criteria.

d) ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

Director, DHA Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. Transmucosal IR Fentanyl Products (TIRFs)

Relative Clinical Effectiveness—The TIRF subclass is comprised of the following formulations of transmucosal fentanyl: oral lozenge (Actiq, generics), buccal tablet (Fentora), sublingual tablet (Abstral), nasal spray (Lazanda), and sublingual spray (Subsys). The soluble buccal film (Onsolis) is no longer marketed. The TIRFs are a subclass of the narcotic analgesics.

All of the TIRFs are indicated for the management of breakthrough cancer pain in patients who are already receiving opioids, and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain. Short-acting opioids also remain a viable option for the treatment of breakthrough cancer pain.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) the following for the TIRF formulations:

1. No head-to-head comparisons of the various TIRF formulations have been conducted to date. Indirect comparisons are difficult to make, due to differences in patient selection criteria, severity of breakthrough pain episodes, and titration as well as repeat dosing protocols.
2. Evidence from a network meta-analysis and a Cochrane systematic review demonstrate that all the TIRFs provide rapid onset of analgesia, with clinically meaningful differences in pain intensity achieved after 30 minutes following administration.
3. Minor pharmacokinetic differences (such as bioavailability and onset of analgesia) do not result in clinically relevant differences in pain relief.
4. Adverse effects are similar for all the TIRFs and are consistent with opioid therapy in cancer patients. Unique application site reactions include dental caries with the lozenge (Actiq) and nasal irritation with the nasal spray (Lazanda).
5. Unique advantages of the products include the following: administration of the lozenge (Actiq) can be interrupted in case of toxicity and it is approved for adolescents 16 years and older. The sublingual tablet (Abstral) and spray (Subsys) have faster dissolution rates than the lozenge (Actiq) and buccal (Fentora) formulations. The nasal spray (Lazanda) is convenient and can be administered by caregivers.
6. Unique disadvantages include the following: the sugar content in the lozenge (Actiq) may cause formation of dental caries and subsequent tooth loss. Lazanda may be unsuitable for patients with respiratory illnesses. Co-administration of Lazanda with a vasoconstrictive nasal decongestant (e.g., oxymetazoline) may lead to reduced fentanyl plasma concentrations.

Overall Clinical-Effectiveness Conclusion—In the absence of direct comparative trials, TIRF selection should be based on individual patient characteristics, likelihood of adherence, and patient preferences.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed to evaluate the TIRF subclass. The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 1 absent) the following:

- CMA results showed that generic fentanyl citrate lozenge (Actiq) was the most cost-effective TIRF, followed by Fentora, Lazanda, and Abstral. Subsys was the least cost effective.
- BIA results showed that all modeled scenarios demonstrated a cost avoidance for the MHS, compared to the current baseline formulary status. The scenario with generic fentanyl lozenge (Actiq) with no step requirement and formulary on the UF, and all other branded agents NF, demonstrated a cost avoidance for the MHS, with the smallest impact to patients from disruption in therapy.

a) ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (9 for, 5 opposed, 1 abstained, 1 absent) the following:

- UF: fentanyl transmucosal lozenge (Actiq, generics)
- NF:
  - Fentanyl sublingual tablet (Abstral)
  - Fentanyl buccal tablet (Fentora)
  - Fentanyl nasal spray (Lazanda)
  - Fentanyl sublingual spray (Subsys)

b) ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) not to add a TIRF to the BCF; morphine sulfate IR will remain the BCF selection for the narcotic analgesics class.

c) ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Abstral, Fentora, Lazanda, and Subsys. See Appendix B for the full criteria.

d) ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

e) ***COMMITTEE ACTION: EXCLUDE FROM 2015 NDAA SECTION 702 REQUIREMENT FOR NF MEDICATIONS AVAILABLE AT MAIL ORDER***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) that the TIRFs recommended for NF status (Abstral, Fentora, Lazanda, and Subsys) be excluded from the requirement that NF drugs be solely available from the TRICARE Mail Order Pharmacy. See Section VIII.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. PAs and MN Criteria

1. **Hepatitis C Virus (HCV) Agents, Direct Acting Antivirals (DAAs): Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir (Viekira Pak) Manual PA Criteria**—The combination product Viekira Pak contains paritaprevir 75 mg, ritonavir 50 mg, and ombitasvir 12.5 mg (dosed two tablets once daily), packaged with dasabuvir 250 mg (dosed twice daily). Viekira Pak was approved by the FDA in December 2014 and is the third FDA-approved interferon-free regimen indicated to treat HCV genotype 1. The hepatitis C drugs will be reviewed at an upcoming meeting.

   a) ***COMMITTEE ACTION: VIEKIRA PAK MANUAL PA CRITERIA***—PA criteria currently apply to the DAAs. The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users of paritaprevir/ritonavir/ombitasvir with dasabuvir (Viekira Pak), consistent with FDA-approved labeling. Prior authorization will expire after 12–24 weeks, based on the treatment regimen. See Appendix C for the full criteria.

2. **Targeted Immunomodulatory Biologics (TIBs): Secukinumab (Cosentyx)** Secukinumab (Cosentyx) is a new TIB indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The TIBs were reviewed by the P&T Committee in August 2014 and automated PA (step therapy) and manual PA criteria were recommended for the class (implemented on December 17, 2014).

   a) ***COMMITTEE ACTION: SECUKINUMAB (COSENTYX) PA CRITERIA*** The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria and step therapy for secukinumab (Cosentyx), consistent with the FDA-approved indication. See Appendix C for the full criteria.

3. **Topical Antifungals: Efinaconazole 10% (Jublia) and Tavaborole 5% (Kerydin) Topical Solutions**—Jublia and Kerydin are indicated for the topical treatment of toenail onychomycosis. Both products are dosed once daily for 48 weeks. The P&T Committee reviewed the current recommended treatment guidelines, FDA-approved indications, efficacy data, safety information, and utilization and cost data for the topical antifungals for toenail onychomycosis.

    a) ***COMMITTEE ACTION: EFINACONAZOLE 10% (JUBLIA) AND TAVABORALE 5% (KERYDIN) MANUAL PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for efinaconazole 10% (Jublia) and tavaborole 5% (Kerydin) in all new and current users of the products. PA criteria were recommended due to the modest efficacy of the products, lack of head-to-head clinical trials, limited efficacy and safety data, and high cost. See Appendix C for the full criteria.

    b) ***COMMITTEE ACTION: EFINACONAZOLE 10% (JUBLIA) AND TAVABORALE 5% (KERYDIN)) PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the PA. Based on the P&T Committee's recommendation, the effective date is August 19, 2015.

4. **Cystic Fibrosis Drugs: Ivacaftor (Kalydeco)**—Ivacaftor (Kalydeco) is indicated for the treatment of cystic fibrosis. PA criteria were recommended at the February 2012 meeting, updated in May 2014, and reflect the FDA-approved indication for various mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In December 2014, Kalydeco received an additional indication for the R117H mutation in the CFTR gene.

    a) ***COMMITTEE ACTION: IVACAFTOR (KALYDECO) MANUAL PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) updated manual PA criteria for Kalydeco to include the expanded FDA-approved indication. See Appendix C for the full criteria.

5. **Non-Insulin Diabetes Mellitus Drugs: Glucagon-Like Peptide-1 Receptor Agonist (GLP1RAs); Exenatide Once Weekly Pen (Bydureon Pen)**—Exenatide (Bydureon) is now available in a pre-filled pen in addition to the original vial formulation. Manual PA criteria were recommended at the November 2014 P&T Committee meeting due to the significant price difference between the Bydureon Pen formulation and the Bydureon vials. The cost of the Bydureon pen is now comparable to the vial formulation.

a) ***COMMITTEE ACTION: EXENATIDE PEN (BYDUREON PEN) REMOVAL OF PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) to remove the manual PA criteria for the Bydureon pen, requiring use of Bydureon vials first. The existing step therapy PA, requiring a trial of metformin or a sulfonylurea first, will remain for the formulation.

6. **Nasal Allergy Drugs: Mometasone (Nasonex) and Fluticasone Furoate (Veramyst) Nasal Inhalers**—The Nasal Allergy Drugs were reviewed by the P&T Committee in May 2014 and automated PA (step therapy) and manual PA criteria were recommended for the class, requiring a trial of generic fluticasone propionate (Flonase) azelastine 137 mcg, flunisolide, or ipratropium. Step therapy does not apply to patients younger than age four. Nasonex and Veramyst were recommended for NF and non step-preferred status. Both drugs are approved for treating symptoms of allergic rhinitis in patients as young as two years of age, while generic Flonase is approved in children as young as four years of age. The P&T Committee recommended updating the MN criteria to reflect the pediatric indications for Nasonex and Veramyst.

   a) ***COMMITTEE ACTION: MOMETASONE (NASONEX) AND FLUTICASONE FUROATE (VERAMYST) MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) revised MN criteria for Nasonex and Veramyst, consistent with the FDA-approved product labeling for use in children as young as two years of age. See Appendix B for the full criteria.

B. QLs—QLs were reviewed for several drugs from the Hepatitis C drugs, inhaled corticosteroids, nasal allergy drugs, antiemetics, and oral chemotherapy drug classes. QLs apply to products in these respective drug classes.

1. ***COMMITTEE ACTIONS: QLs***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) QLs for paritaprevir/ritonavir/ombitasvir dasabuvir (Viekira Pak), fluticasone furoate inhaler (Arnuity Ellipta), beclomethasone hydrofluoroalkane (HFA) pediatric 40 mcg/spray (QNASL), netupitant/palonosetron (Akynzeo), and olaparib (Lynparza), consistent with the product labeling. See Appendix E for QLs.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VII. LINE EXTENSIONS

A. Formulary Status Clarification—The P&T Committee clarified the formulary status for one product line extension ("follow-on product") by the original manufacturer. Line extensions have the same FDA indications and pricing as the "parent" drug.

1. ***COMMITTEE ACTION: LINE EXTENSIONS FORMULARY STATUS CLARIFICATION***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) clarifying the formulary status of beclomethasone HFA nasal spray 40 mcg/spray (Children's QNASL). The 40 mcg/spray is a new formulation approved for children aged 4–11 years. Children's QNASL is recommended to have the same formulary status as the 80 mcg/spray formulation (QNASAL), which is indicated for adults and children older than 12 years. Implementation will occur upon signing of the minutes.

    - Beclomethasone HFA nasal spray 40 mcg/spray (Children's QNASL): NF and non step-preferred, similar to beclomethasone HFA nasal spray 80 mcg/spray (QNASL). The same step therapy criteria and manual PA criteria will apply.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. 2015 National Defense Authorization Act (NDAA) Section 702

A. NF Medications Available at Mail Order Pharmacy Only—The P&T Committee was briefed on the following four components in 2015 NDAA Section 702 impacting the pharmacy benefit:

- co-pay changes,
- generic drugs to NF tier,
- termination of the TRICARE For Life pilot, subsequently making the program permanent and expanding to under 65, and
- NF medications available at the Mail Order Pharmacy only.

The 2015 NDAA, signed in December 2014, restricts the availability of NF drugs to one point of service, the Mail Order Pharmacy. Beneficiaries with medical necessity will be able to obtain NF drugs at other points of service at the UF co-pay.

This law takes effect with decisions made during the 2015 P&T Committee meetings. Drugs designated with NF status by the P&T Committee will be restricted to the Mail Order Pharmacy. However, an additional vote by the P&T Committee is required for certain drugs (including those for acute therapy, schedule II controlled substances, antipsychotics, oncology agents, and limited distribution drugs) to be excluded from the requirement that NF drugs be

solely available from the Mail Order Pharmacy. Emergent overrides (e.g., drug shortages, special circumstances or emergencies, natural disasters) will be allowed.

PA criteria were recommended to ensure patient safety. Additionally, the P&T Committee requested a 90-day PA expiration for patients meeting the titration criteria listed in (c), below. This request will be evaluated and implemented when operationally feasible.

1. ***COMMITTEE ACTION: NF PRESCRIPTIONS MANUAL PA CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) manual PA criteria for all new NF prescriptions. Coverage will be approved if the prescriber provides the following information listed below.

   a) Does the patient reside in a long-term care facility?

   b) Does the patient have barriers to receiving medications by mail (e.g., no permanent mail address, resides in a rural setting)?

   c) Is the patient not on a stable dose of medication or is the medication currently being titrated?

Director, DHA Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

IX. ITEMS FOR INFORMATION

A. New Drugs Go to Third Tier—The current 32 Code of Federal Regulations (CFR) Part 199 statute states that new FDA-approved drugs are immediately placed on the Second Tier (formulary brand-name drugs).

The Proposed Pharmacy TRICARE Rule, published in the CFR on September 19, 2014, clarifies the process for formulary placement of newly approved innovator drugs brought to market under a New Drug Application approved by the FDA. The proposed rule provides the P&T Committee up to 120 days to recommend tier placement on the UF. During this 120-day period, new drugs would be assigned a "pending status" and be available in the Retail Network and Mail Order Pharmacy under terms comparable to NF (Third Tier) drugs. Tier classification will normally occur at the next P&T Committee meeting following FDA approval. The rule is available at http://www.gpo.gov/fdsys/pkg/FR-2014-09-19/pdf/2014-22276.pdf.

X. ADJOURNMENT

The meeting adjourned at 1130 hours on February 12, 2015. The next meeting will be in May 2015.

Appendix A—Attendance: February 2015 P&T Committee Meeting
Appendix B—Table of Medical Necessity Criteria
Appendix C—Table of Prior Authorization Criteria
Appendix D—Table of Prior Authorization Criteria for Hepatitis C Drugs
Appendix E—Table of Quantity Limits
Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary
Appendix G—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

5 May 2015
Date

Appendix A—Attendance: February 2015 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CAPT Nita Sood	Chief of Staff, DHA Pharmacy Operations Division
CAPT Walter Downs, MC	Chief, DHA Formulary Management Branch (Recorder)
COL John Spain, MS	Army, Pharmacy Officer
Col Scott Sprenger, BSC	Air Force, Pharmacy Officer
CDR Aaron Middlekauf, USCG	Coast Guard, Pharmacy Officer Alternate
CAPT Thinh Ha, MSC	Navy, Pharmacy Officer
MAJ John Poulin, MC	Army, Physician at Large
Col Michael Wynn, MC	Army, Family Practice Physician
Col James Jablonski, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Larissa Weir, MC	Air Force, OB/GYN Physician
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Voting Members Absent	
George Jones, PharmD, M.S.	Chief, DHA Pharmacy Operations Division
Col Michael Spilker, BSC	DHA Deputy Chief, Pharmacy Operations Division
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present	
Mr. Bryan Wheeler	Deputy General Counsel, DHA
Guests	
Mr. Bill Davies via DCO	DHA Pharmacy Operations Division
MAJ Kevin Ridderhoff, MS	DHA, Pharmacy Operations Division
Lt Col Ann McManis via DCO	DHA, Pharmacy Operations Division
LCDR Robert Selvester, MC	VA/DoD Evidence-Based Practice Guideline Work Group
Mr. Matthew Lechtenberg	VA Pharmacy Benefit Management

Appendix A—Attendance (continued)

Guests	
Mr. Alexander Quinones	Defense Logistics Agency Troop Support
MAJ Randall Sweeney	Defense Logistics Agency Troop Support
CDR Matthew Baker	Indian Health Service
Mr. Emmett Larson	DHA Contract Operations Division
Mr. Matthew Gilger	DHA Contract Operations Division
Others Present	
LTC Robert Conrad, MS via phone	DHA Pharmacy Operations Division
LCDR Marisol Martinez, USPHS	DHA Pharmacy Operations Division
LTC Misty Cowan, MC	DHA Pharmacy Operations Division
Maj David Folmar, BSC	DHA Pharmacy Operations Division
Maj Ronald Khoury, MC	DHA Pharmacy Operations Division
CDR Edward Vonberg, BSC	DHA Pharmacy Operations Division
Angela Allerman, PharmD, BCPS	DHA Pharmacy Operations Division
Shana Trice, PharmD, BCPS	DHA Pharmacy Operations Division
Amy Lugo, PharmD, BCPS via DCO	DHA Pharmacy Operations Division
Teresa Anekwe, PharmD, BCPS via DCO	DHA Pharmacy Operations Division
Brian Beck, PharmD, BCPS	DHA Pharmacy Operations Division
David Meade, PharmD, BCPS via phone	DHA Pharmacy Operations Division
Ms. Deborah Garcia	DHA Pharmacy Operations Division contractor
Mr. Kirk Stocker	DHA Pharmacy Operations Division contractor
Esmond Nwokeji, PhD	DHA Pharmacy Operations Division contractor
Maj Ellen Roska	University of Texas PhD student
Brittny Wolda	Incarnate Word Pharmacy student

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Tasimelteon (Hetlioz) **Sedative Hypnotic-1s (SED-1s)**	• No alternative formulary agent – patient is blind and has non-24 sleep wake disorder **Formulary alternatives:** melatonin supplement, zolpidem IR, zaleplon, eszopiclone
• Empagliflozin (Jardiance) **Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors**	• Use of the formulary agent is contraindicated **Formulary alternatives:** metformin, sulfonylureas, sitagliptin (Januvia, Janumet), linagliptin (Tradjenta, Jentadueto), GLP1RAs, pioglitazone, insulin
• Vorapaxar (Zontivity) **Antiplatelet Agents**	• Formulary agents result or are likely to result in therapeutic failure. **Formulary alternatives:** clopidogrel, cilostazol, pentoxifylline, dipyridamole, Aggrenox, prasugrel, ticagrelor
• Avanafil (Stendra) **PDE-5 Inhibitors for Erectile Dysfunction**	• Use of formulary agents is contraindicated • Patient has experienced or is likely to experience significant adverse effects from formulary agents • Formulary agents result or are likely to result in therapeutic failure **Formulary alternative:** sildenafil (Viagra)
• Esomeprazole Strontium **Proton Pump Inhibitors (PPIs)**	• Use of ALL formulary agents is contraindicated • Patient has experienced or is likely to experience significant adverse effects from ALL formulary agents • All formulary agents result or are likely to result in therapeutic failure **Formulary alternatives:** omeprazole (Prilosec, generics), pantoprazole tablets (Protonix, generics), and esomeprazole magnesium (Nexium)
• Fentanyl sublingual tablet (Abstral) • Fentanyl buccal tablet (Fentora) • Fentanyl nasal spray (Lazanda) • Fentanyl sublingual spray (Subsys) **Transmucosal Immediate Release Fentanyl Products (TIRFs)**	• Use of formulary agents is contraindicated • Patient has experienced or is likely to experience significant adverse effects from formulary agents o For example, dental caries with Actiq or uncontrolled diabetic patients requiring sugar-free formulations • Patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk o For example, patient has xerostomia or mucositis and requires non-oral route of administration • **Formulary alternatives:** fentanyl citrate lozenge, morphine sulfate IR, oxycodone IR, oxymorphone IR, hydromorphone IR

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Tasimelteon (Hetlioz) **Newer Sedative Hypnotics (SED-1s)**	The previous automated (step therapy) criteria for tasimelteon (Hetlioz) (requiring a trial of zolpidem IR or zaleplon) no longer apply. Manual PA criteria apply to all new users of tasimelteon (Hetlioz). Manual PA criteria: Tasimelteon (Hetlioz) is approved if: i. The patient is totally blind and has a documented diagnosis of non-24 sleep wake disorder AND ii. The patient has had a trial of melatonin and either failed or had an adverse event AND iii. The patient is not taking a drug that will interact with tasimelteon (i.e., beta blockers or strong CYP3A4 inducers) PA Criteria will expire after 6 months (if patient has not responded after 6 months, they will be deemed a non-responder)
• Empagliflozin (Jardiance) **Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors**	All new and current users of empagliflozin (Jardiance) are required to try metformin or a sulfonylurea (SU), and a dipeptidyl-dipeptidase-4 (DPP-4) inhibitor before empagliflozin (Jardiance). Automated PA criteria: The patient has filled a prescription for metformin or a SU, AND a DPP-4 inhibitor at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, empagliflozin (Jardiance) is approved (e.g., trial of metformin or SU AND a DPP-4 inhibitor is NOT required) if: • The patient has experienced any of the following issues on metformin: o impaired renal function precluding treatment with metformin o history of lactic acidosis • The patient has experienced any of the following issues on a sulfonylurea: o hypoglycemia requiring medical treatment • The patient has had inadequate response to metformin or a SU or a DPP-4 inhibitor • The patient has a contraindication to metformin or a SU or DPP-4 inhibitor

Drug / Drug Class	Prior Authorization Criteria
• Avanafil (Stendra) **PDE-5 Inhibitors for Erectile Dysfunction (ED)**	PA criteria apply to all current users of avanafil. Automated PA criteria: Coverage approved for treatment of ED if: a) The patient has received a prescription for sildenafil (Viagra) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days, AND b) The patient is a male aged 40 years or older. Manual PA criteria: A trial of sildenafil (Viagra) is not required if: • Patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects. • Treatment with sildenafil (Viagra) is contraindicated. • Patient is between 18 and 39 years of age and is being treated for ED of organic or mixed organic/psychogenic origin. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in a) or b).] • Patient is between 18 and 39 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in a) or b).] Coverage is approved for the following non-ED uses requiring daily therapy: • Use of sildenafil, tadalafil, or avanafil (Stendra) for preservation/restoration of erectile dysfunction after prostatectomy. PA expires after one year.
• Esomeprazole Strontium **Proton Pump Inhibitors (PPIs)**	PA criteria apply to all new and current users of esomeprazole strontium. Automated PA criteria: The patient has filled a prescription for omeprazole (Prilosec, generics), pantoprazole tablets (Protonix, generics), or esomeprazole magnesium (Nexium) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order), during the previously 180 days. AND Manual PA criteria: A trial of omeprazole (Prilosec, generics), pantoprazole tablets (Protonix, generics), or esomeprazole magnesium (Nexium) is NOT required if: • The patient has tried omeprazole, pantoprazole tablets, and esomeprazole magnesium (Nexium) and had an inadequate response. • The patient has tried omeprazole, pantoprazole tablets, and esomeprazole magnesium (Nexium) and was unable to tolerate it due to adverse effects. • Treatment with omeprazole, pantoprazole tablets, and esomeprazole magnesium (Nexium) is contraindicated (e.g., hypersensitivity; moderate to severe hepatic insufficiency).

Drug / Drug Class	Prior Authorization Criteria
• Sildenafil 20mg generic • Sildenafil brand (Revatio) • Tadalafil (Adcirca) • Riociguat (Adempas) **Pulmonary Arterial Hypertension Agents (PAH) – Nitric Oxide Drugs Subclass**	PA criteria apply to all new users of Adempas and Adcirca. Automated PA criteria: The patient has filled a prescription for sildenafil 20mg generic or sildenafil brand (Revatio) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: Adempas and Adcirca is approved (e.g., a trial of sildenafil is NOT required) if: • For Adempas: o Patient has a documented diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) o Patient has tried a PDE-5 inhibitor and failed or did not respond to therapy o Patient has experienced significant adverse effects from the PDE-5 inhibitor • For Adcirca: o Patient has tried a sildenafil 20 mg generic or sildenafil brand (Revatio) and failed or did not respond to therapy • For both Adempas and Adcirca: o Patient is not taking a nitrate drug.
• Enzalutamide (Xtandi) **Prostate Cancer Drugs Subclass II – Survival Prolonging Drugs**	Coverage is approved if: • Documented diagnosis of metastatic castration-resistant prostate cancer No expiration date for the PA
• Abiraterone (Zytiga) **Prostate Cancer Drugs Subclass II – Survival Prolonging Drugs**	Coverage is approved if: • Documented diagnosis of metastatic castration-resistant prostate cancer AND • Patient is receiving concomitant therapy with prednisone. No expiration date for the PA
• Nilutamide (Nilandron) **Prostate Cancer Subclass I – Anti-Androgens**	Manual PA criteria: PA criteria apply to all new users of nilutamide. Nilutamide is approved if any of the following: • Patient has experienced significant adverse effects or contraindication from bicalutamide or flutamide; or • Patient has experienced therapeutic failure with bicalutamide or flutamide; or • Patient has a diagnosis of metastatic prostate cancer (stage D2) disease and the patient has undergone orchiectomy.

Drug / Drug Class	Prior Authorization Criteria
• Secukinumab (Cosentyx) **Targeted Immunomodulatory Biologics (TIBs)**	PA criteria apply to all new and current users of Cosentyx. Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days AND Manual PA criteria: If automated criteria are not met, coverage is approved for Cosentyx if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB AND Coverage approved for patients > 18 years with: • Active moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy Coverage is NOT provided for concomitant use with other TIBs.
• Efinaconazole 10% (Jublia) and tavaborole 5% (Kerydin) Topical Solutions **Topical Antifungals**	PA criteria apply to all new and current users of Jublia and Kerydin. Manual PA criteria: Jublia and Kerydin are approved if all of the following criteria apply: 1. The patient must have diagnostically confirmed onychomycosis by either KOH preparation, fungal culture, nail biopsy, or other assessment to confirm diagnosis. 2. The patient is immunocompromised, has diabetes mellitus, or peripheral vascular disease and has swelling and/or redness in the surrounding nail tissue or pain in affected nail(s). 3. The patient has history of one of the following (therapeutic failure, contraindication or adverse events, or intolerance) to one of the following antifungals: itraconazole, terbinafine, or ciclopirox • therapeutic failure • contraindication (e.g., renal impairment, pre-existing liver disease, or evidence of ventricular dysfunction such as CHF) • adverse event/intolerance to one of the following antifungal agents 4. Treatment is requested due to a medical condition and not for cosmetic purposes. Examples include the following: • patients with history of cellulitis of the lower extremity who have ipsilateral toenail onychomycosis • diabetic patients with additional risk factors for cellulitis • patients who experience pain/discomfort associated with the infected nail 5. The patient's condition is causing debility or a disruption in their activities of daily living. 6. Jublia or Kerydin have not been used in the previous 24 months. PA nilutamide expires after 1 year.

Drug / Drug Class	Prior Authorization Criteria
• Ivacaftor (Kalydeco) **Cystic Fibrosis Drugs**	Manual PA Criteria apply to all new and current users of Ivacaftor (Kalydeco). 1. Coverage will be approved for the treatment of CF patients aged 6 years and older who have a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or for R117H mutation in the CFTR gene, detected by an FDA-approved test. 2. Coverage is not approved for patients who are homozygous for the F508del mutation in the CFTR gene.
• Exenatide once weekly pen (Bydureon pen) **Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)**	Manual PA criteria from the November 2014 meeting recommended to be removed. Exenatide once weekly (Bydureon pen) • Coverage approved if patient has first tried Bydureon 2mg vial/cartridge first AND • Patient has dexterity issues and cannot assemble the Bydureon vial/cartridge

Appendix D—Table of Prior Authorization (PA) Criteria for Hepatitis C Drugs

Prior Authorization Criteria

Paritaprevir/ritonavir/ombitasvir with dasabuvir (Viekira Pak)
Direct Acting Antiviral Subclass

- New users of paritaprevir/ritonavir/ombitasvir with dasabuvir (Viekira Pak) are required to undergo the PA process.
- Current users are not affected by PA; they can continue therapy uninterrupted.
- Patients are encouraged to use the Mail Order Pharmacy or MTFs to fill their Viekira Pak prescriptions.
- Consult the AASLD/IDSA HCV guidelines (www.hcvguidelines.org) for the most up-to-date and comprehensive treatment for HCV. Unique patient populations are also addressed and treatment recommendations may differ from those for the general population.

Manual PA Criteria:

- Age ≥ 18
- Has laboratory evidence of chronic HCV genotype 1 infection
    1. State the HCV genotype and HCV RNA viral load on the PA form
- Paritaprevir/ritonavir/ombitasvir + dasabuvir (Viekira Pak) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.
- The patient is not co-infected with Hepatitis B virus (HBV).

Treatment Regimens and Duration of Therapy

- Treatment and duration of therapy are approved for one of the following regimens outlined below, based on HCV genotype, prior treatment, and presence of cirrhosis.
- Prior authorization will expire after 12 weeks or 24 weeks, based on the treatment regimen selected.

Genotype 1 Patient Populations[1,2]	***Treatment***	***Duration***
GT1a without cirrhosis	Viekira Pak + ribavirin bid	12 weeks
GT1a with cirrhosis	Viekira Pak + ribavirin bid	24 weeks[3]
GT1b without cirrhosis	Viekira Pak	12 weeks
GT1b with cirrhosis	Viekira Pak + ribavirin bid	12 weeks
Liver transplant recipients with normal hepatic function and mild fibrosis (Metavir ≤2)	Viekira Pak + ribavirin bid	24 weeks

[1]Follow GT1a dosing recommendation in patients with an unknown GT1 or mixed GT1 infection
[2]Treatment naïve or treatment-experienced with peginterferon alpha plus ribavirin
[3]For treatment naïve OR prior IFN+RBV relapser/partial responder, consider 12 weeks

Appendix E—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
• Avanafil (Stendra) **PDE-5 Inhibitors**	• Retail and MTF Network: 6 tablets per 30 days (collective of all PDE-5 inhibitors) • Mail Order Pharmacy: 18 tablets per 90 days (collective of all PDE-5 inhibitors)
• Paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak) **Hepatitis C Drugs**	• Retail Network, Mail Order and MTF: 4 Paks /28 days • Each Viekira Pak contains 7 individual packages and provides for daily dosing for one week • Individual packages contain 2 paritaprevir/ritonavir/ombitasvir tablets and 2 dasabuvir tablets
• Fluticasone furoate oral inhaler (Arnuity Ellipta) **Inhaled Corticosteroid**	• Retail: 60 blisters (1 Diskus)/30 days • MTF and Mail: 180 blisters (3 Diskus)/90 days
• Beclomethasone HFA pediatric nasal spray (QNASL) 40 mcg **Nasal Allergy Drug**	• Retail: 1 canister/30 days • MTF and Mail: 3 canisters/90 days
• Netupitant/palonosetron (Akynzeo) 300 mg/0.5 mg cap **Antiemetic**	• Retail: 2 boxes/30 days • MTF and Mail: 6 boxes/90 days
• Olaparib (Lynparza) 50 mg cap **Oral Oncology Drug (Ovarian Cancer)**	• Retail: 448 caps (4 bottles)/28 days • MTF and Mail: 896 caps (8 bottles)/56 days

Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2015	**Pulmonary Arterial Hypertension (PAH) Agents**	UF class review Not previously reviewed (PDE-5 inhibitors for PAH reviewed Nov 2009)	▪ ECF: Sildenafil 20 mg (generic) and sildenafil brand (Revatio)	*Nitric oxide pathway:* *Step preferred:* ▪ sildenafil 20mg generic ▪ sildenafil brand (Revatio) *Non step-preferred* ▪ tadalafil (Adcirca) ▪ riociguat (Adempas) *Endothelin receptor antagonists:* ▪ bosentan (Tracleer) ▪ ambrisentan (Letairis) ▪ macitentan (Opsumit) *Prostacyclins:* ▪ treprostinil nebulized solution (Tyvaso) ▪ treprostinil tabs (Orenitram ER) ▪ iloprost nebulized solution (Ventavis)	▪ None	Pending singing of the minutes / 90 days	▪Step therapy required for the nitric oxide agents; see comments	▪ For the nitric oxide pathway drugs, a trial of sildenafil 20 mg generic or sildenafil brand (Revatio) is required prior to Adcirca or Adempas. See Appendix C. ▪ Adcirca was previously NF, but now is UF, and non step-preferred.
Feb 2015	**Prostate Cancer Drugs**	UF class review	▪ Bicalutamide (Casodex)	▪ Flutamide (Eulexin) ▪ Nilutamide (Nilandron) ▪ Enzalutamide (Xtandi) ▪ Abiraterone (Zytiga)	▪ None	Pending singing of the minutes / 90 days	▪PA required for nilutamide (See Appendix C)	▪ Bicalutamide is now BCF. ▪ No change recommended for the current PA for Zytiga and Xtandi

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2015	**Transmucosal Immediate Release Fentanyl Products (TIRFs)**	UF subclass review Not Previously reviewed	▪ None (see Comments)	▪ Fentanyl transmucosal lozenge (Actiq, generics)	▪ Fentanyl sublingual tablet (Abstral) ▪ Fentanyl buccal tablet (Fentora) ▪ Fentanyl nasal spray (Lazanda) ▪ Fentanyl sublingual spray (Subsys)	Pending singing of the minutes / 90 days	▪ High opioid safety edit in place	▪ No BCF selection for this subclass ▪ This is a subclass of the High Potency narcotic drugs; morphine sulfate IR and controlled release morphine sulfate (MS Contin, generics) are designated BCF
Feb 2015	**Newer Sedative Hypnotics (SED-1s)**	New Drug	▪ Zolpidem immediate-release	*Step preferred* ▪ Zaleplon (Sonata) *Non step-preferred* ▪ Zolpidem ER (Ambien CR) ▪ Eszopiclone (Lunesta) ▪ Doxepin (Silenor)	▪ **Tasimelteon (Hetlioz) February 2015** ▪ Ramelteon (Rozerem) ▪ Zolpidem SL (Edluar) ▪ Zolpidem SL (Intermezzo)	Pending signing of the minutes / 60 days	▪ Step therapy (automated PA); requires a trial of zolpidem IR or zaleplon for all SED-1 agents except tasimelteon	▪ All new users of Hetlioz will undergo a manual PA process ▪ See Appendix C for Manual PA criteria.

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2015	**Non-Insulin Diabetes Drugs: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**	New Drug	▪ None (see comments)	▪ None (see comments)	▪ **Empagliflozin (Jardiance) February 2015** ▪ Dapagliflozin (Farxiga) May 2014 ▪ Canagliflozin (Invokana)	Pending signing of the minutes / 90 days	▪ Step therapy (automated PA); requires a trial of metformin, or sulfonylureas (SUs), and a DPP-4 inhibitor in all new and current users of a SGLT2 inhibitor.	▪ BCF, UF, and NF drugs are designated for metformin, SUs, DPP-4 inhibitors, GLP-1RAs, TZDs, meglitinides, and alpha glucosidase inhibitors. See DoD P&T Minutes for Nov 2010, Aug 2012, and Nov 2012.
Feb 2015	**Antiplatelet Agents**	New Drug Review	▪ Clopidogrel (Plavix)	▪ Prasugrel (Effient) ▪ Ticagrelor (Brilinta) ▪ Aspirin/dipyridamole ER (Aggrenox) ▪ Ticlopidine (Ticlid, generics) ▪ Cilostazol (Pletal, generics) ▪ Dipyridamole (Persantine, generics) ▪ Pentoxifylline (Trental, generics)	▪ **Vorapaxar (Zontivity) February 2015**	Pending signing of the minutes / 90 days	▪ N/A	▪ None

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2015	**PDE-5 Inhibitors for Erectile Dysfunctions**	New Drug Review	▪ Sildenafil (Viagra)	▪ None for Erectile Dysfunction	▪ **Avanafil (Stendra) February 2015** ▪ Tadalafil (Cialis) ▪ Vardenafil (Levitra, Staxyn)	Pending singing of the minutes / 90 days	▪PA required for Stendra (See Appendix C) ▪QL apply – see Appendix E	▪ Viagra is the BCF and step-preferred PDE-5 inhibitor for erectile dysfunction.
Feb 2015	**Proton Pump Inhibitors**	New Drug Review	▪ Omeprazole (Prilosec, generic) excludes 40mg Prilosec capsule ▪ Esomeprazole (Nexium)	▪ Prilosec 40mg (brand) ▪ Pantoprazole (Protonix, generic) tablets	▪ **Esomeprazole strontium (February 2015)** ▪ Lansoprazole (Prevacid) ▪ Omeprazole NaHCO3 (Zegerid) ▪ Rabeprazole (Aciphex) ▪ Dexlansoprazole (Dexilant)	Pending signing of the minutes / 90 days	▪PA applies (See Appendix C)	▪ See DoD P&T Minutes for Nov 2012, May 2009, Feb 2008, & May 2007

TRICARE Formulary Search tool: *http://www.pec.ha.osd.mil/formulary_search.php*

Appendix G—Table of Abbreviations

6MWD	6-minute walking distance
A1c	hemoglobin A1c
AASLD/IDSA	American Association for the Study of Liver Diseases/Infectious Diseases Society of America
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
CMA	cost minimization analysis
CTEPH	chronic thromboembolic pulmonary hypertension
CV	cardiovascular
DAAs	direct acting antivirals
DCO	Defense Connect Online
DHA	Defense Health Agency
DoD	Department of Defense
DPP-4	dipeptidyl dipeptidase-4 inhibitors
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
ERA	endothelin receptor agonists
FDA	U.S. Food and Drug Administration
GLP1RA	glucagon-like peptide-1 receptor agonist
HCV	hepatitis C virus
HFA	hydrofluoroalkane
IR	immediate release
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
NDAA	National Defense Authorization Act
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAH	Pulmonary Arterial Hypertension Drug Class
PDE-5	Phosphodiesterase-5 Inhibitors Drug Class
PPIs	proton pump inhibitors
POS	points of service
QLs	quantity limits
SED-1s	Sedative Hypnotic-1s Drug Class
SGLT2	Sodium-Glucose Co-Transporter 2 Inhibitors Drug Class
TIBs	targeted immunomodulatory biologics
TIRFs	transmucosal IR fentanyl products
UF	Uniform Formulary

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

November 2014

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on November 19 and 20, 2014, at the Defense Health Agency (DHA) Formulary Management Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Lt. Gen. Douglas J. Robb, DO, MPH, Director, DHA, approved the minutes from the August 2014 DoD P&T Committee meeting on November 13, 2014.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Insulin Drugs: Miscellaneous Insulin Delivery Devices—Valeritas V-Go (V-Go)

Background—V-Go is a disposable insulin delivery device approved for patients with diabetes mellitus. Unlike an insulin pump, V-Go does not require any tubing or catheters. The device is filled daily with rapid-acting insulin, allowing for continuous administration of basal insulin and optional bolus dosing. After 24 hours, the device is discarded and replaced with a new unit.

The advantages of using V-Go include convenience for the patient who desires increased control over their blood glucose levels and elimination of the need for multiple daily insulin injections. Compared to multiple insulin injections, V-Go may reduce prandial glycemic excursions.

There are no randomized controlled trials using the V-Go insulin delivery device compared to usual care with basal or basal/bolus insulin dosing using pens or vials. Limitations of the V-Go studies include small sample sizes (<140 patients enrolled), varied efficacy endpoints, short trial duration, and lack of published studies. Another limitation is that reports of patients requiring overall reduced total daily insulin doses was based on subjective patient-reported data and not on objective endpoints. Additionally, the discontinuation rates in the V-Go studies were high. Although the V-Go studies reported improvements in hemoglobin A1c- lowering, it is difficult to attribute those improvements to the V-Go device due to the lack of control groups and limitations in study design. Long-term data on whether the V-Go device improves patient adherence is lacking.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that the V-Go delivery device offers patient convenience because multiple daily insulin injections are not needed; however, it offers no clinically compelling advantages over existing UF insulin agents administered with pens or vials.

Relative Cost-Effectiveness Analysis and Conclusion—Cost-minimization analysis (CMA) was performed. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that the CMA showed V-Go was more costly than other combinations of basal/bolus insulin (e.g., Lantus/Novolog) currently on the UF.

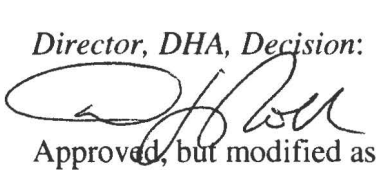
1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) V-Go be designated NF due to the lack of compelling clinical advantages and the cost disadvantage compared to the other UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for V-Go. See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** Manual PA criteria were recommended at the August 2014 DoD P&T Committee meeting and implemented on November 14, 2014. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) clarifying the PA criteria for V-Go. See Appendix C for the full criteria.

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS). Based on the P&T Committee's recommendation, the effective date is April 8, 2015.

Director, DHA, Decision: ☒ Approved ☐ Disapproved



Approved, but modified as follows:

B. Chronic Obstructive Pulmonary Disease (COPD) Drugs—Umeclidinium/Vilanterol (Anoro Ellipta)

Background—Umeclidinium/vilanterol is the first fixed dose combination of a long-acting muscarinic agent (LAMA) with a long-acting beta agonist (LABA) to reach the market. Anoro Ellipta is indicated for maintenance treatment of COPD; in contrast, other products have the additional indication for reducing COPD exacerbations (Spiriva, Advair, and Breo Ellipta).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the main clinical benefits of umeclidinium/vilanterol are its superior improvements in forced expiration volume in 1 second (FEV_1) compared to single ingredient inhalers, the convenience to patients of combining two long-acting bronchodilators into one inhaler, and once daily dosing. The COPD agents will be re-reviewed at an upcoming meeting for UF and BCF placement. Additionally, the P&T Committee recommended adding the LAMA/LABA combinations to the Pulmonary II Drug Class, which includes other chemical entities used for treating COPD.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate umeclidinium/vilanterol (Anoro Ellipta) with other LAMA and LABA therapies in the treatment of COPD. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA showed that the Anoro Ellipta fixed dose combination bronchodilator offers a cost-effective alternative to combining available LAMA and LABA inhalers.

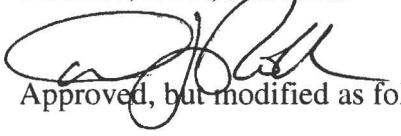
1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) umeclidinium/vilanterol (Anoro Ellipta) be designated formulary on the UF, based on clinical and cost effectiveness.

2. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following QLs for umeclidinium/vilanterol (Anoro Ellipta), consistent with the FDA-approved package labeling:

    - Retail Network: 1 inhaler per 30 days
    - Mail Order Pharmacy: 3 inhalers per 90 days

3. ***COMMITTEE ACTION: TRICARE FOR LIFE PHARMACY DRUG LIST***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) adding Anoro Ellipta to the TRICARE for Life Pharmacy Drug List due to the potential for additional cost avoidance, and for consistency with other inhaled bronchodilators on the UF that are already included on the Pharmacy Drug List.

Director, DHA, Decision: ☑ Approved □ Disapprov



Approved, but modified as follows:

C. Glaucoma Drugs: Brinzolamide 1%/Brimonidine 0.2% Ophthalmic Suspension (Simbrinza)

Background—Brinzolamide/brimonidine ophthalmic suspension (Simbrinza) is the first fixed dose combination product for glaucoma that has components other than a beta blocker. It contains a carbonic anhydrase inhibitor (brinzolamide, Azopt) and an alpha 2 adrenergic receptor agonist (brimonidine, Alphagan).

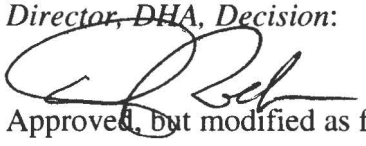
Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) Simbrinza's fixed combination offers a convenience to the patient versus using two drugs concomitantly, even though it requires dosing three times a day. Simbriniza also decreases intraocular pressure to a greater extent than the individual components administered alone.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate brinzolamide/brimonidine (Simbrinza) with other drugs used in the treatment of glaucoma. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA showed that brinzolamide/brimonidine (Simbrinza) was comparable to the UF carbonic anhydrase inhibitors and alpha 2 adrenergic receptor agonists when taken in combination.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) brinzolamide 1%/brimonidine 0.2% ophthalmic suspension (Simbrinza) be designated with formulary status on the UF, based on clinical and cost effectiveness.

Director, DHA, Decision: ☑ Approved □ Disapproved



Approved, but modified as follows:

D. Ophthalmic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)—Bromfenac 0.07% Ophthalmic Solution (Prolensa)

Background—Bromfenac 0.07% (Prolensa) is FDA-indicated for the treatment of postoperative inflammation and pain in patients following cataract surgery. It is the third bromfenac formulation to obtain FDA approval. The branded formulations of bromfenac 0.09% (Xibrom)

dosed twice daily and bromfenac 0.09% (Bromday) dosed once daily (QD) have been discontinued by the manufacturer.

There are no head-to-head clinical trials comparing Prolensa with another ophthalmic NSAID. There is no data to show that Prolensa is better tolerated when compared to generic bromfenac 0.09% (Bromday) QD. While Prolensa offers the convenience of once daily dosing, generic Bromday is also dosed once daily.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that Prolensa does not offer clinically relevant advantages over the other UF ocular NSAIDs that are FDA-approved for use following cataract surgery.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate bromfenac 0.07% ophthalmic solution (Prolensa) with other ophthalmic NSAIDs on the UF. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that Prolensa was the most costly ocular NSAID.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) bromfenac 0.07% ophthalmic solution (Prolensa) be designated NF due to the lack of compelling clinical advantages and the cost disadvantage compared to the other UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for bromfenac 0.07% ophthalmic solution (Prolensa). See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is May 6, 2015.

Director, DHA Decision ☑ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Self-Monitoring Blood Glucose System (SMBGS) Test Strips

Background—The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips. See Appendix D for a full list of the SMBGS test strips in the class. SMBGS

glucometers are not included as part of the TRICARE outpatient pharmacy benefit (they are included under the medical benefit) and are not the focus of the review.

U.S. Federal Government contracting requirements stated the following:

> The Company shall ensure test strips are made available to all three Points of Service (Military Treatment Facilities, TRICARE Mail Order Pharmacy, and Retail Network). In accordance with industry practice, the Company shall make meters available to DoD beneficiaries at no additional charge or cost to the DoD beneficiary.

The FDA classifies SMBGS test strips and glucometers as medical devices rather than drugs. The clinical effectiveness review focused on differences in the technical aspects/attributes among the test strips and glucometers. The P&T Committee recommended that the potential test strips considered for inclusion on the UF should meet standards relating to such factors as FDA requirements for accuracy based on the International Organization for Standardization (ISO) 15197 guidelines from 2003, sample size, alternate site testing, result time, memory capacity, ease of calibration, customer support, downloading capabilities, and data management capabilities.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following for the SMBGS test strips:

- Potential SMBGS test strips considered for inclusion on the UF must meet all U.S. Federal Government contracting requirements and the technical factors listed above.
- Potential SMBGS test strips considered for inclusion on the UF included FreeStyle Lite; FreeStyle InsuLinx; Precision Xtra; ACCU-CHEK Aviva Plus; OneTouch Ultra Blue; OneTouch Verio; CONTOUR NEXT; TRUEtest; Nova Max; GLUCOCARD 01-SENSOR; GLUCOCARD Vital; and Prodigy No Coding.
- *Overall relative clinical effectiveness conclusion:* The P&T Committee concluded there were no clinically relevant differences between the 12 SMBGS test strips that were reviewed and met the contracting requirements and technical factors, and that any of the 12 test strips were acceptable for inclusion on the UF.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and budget impact analysis (BIA) were performed to evaluate the SMBGS test strips that were considered for inclusion on the UF. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- Results from a comprehensive cost analysis, which included a CMA and considered the cost of patient switching and related DoD administrative costs in addition to SMBGS test strip per unit costs, showed FreeStyle Lite and Precision Xtra test strips were the most cost-effective SMBGS test strips, followed by ACCU-CHEK Aviva Plus, GLUCOCARD Vital and GLUCOCARD 01-SENSOR, TRUEtest, Prodigy No Coding, CONTOUR NEXT, Nova Max, and all other SMBGS test strips. OneTouch Ultra Blue test strips were the least cost-effective.

- BIA was performed to evaluate the potential impact of scenarios, with selected test strips designated step-preferred and UF or non-preferred and NF on the UF. BIA results showed the scenario with FreeStyle Lite and Precision Xtra designated as step-preferred on the UF and all remaining test strips designated NF and non-step preferred, where all current and new users are required to try FreeStyle Lite or Precision Xtra first, was the most cost-effective option for the Military Health System (MHS).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following:

    - UF and step-preferred:
        - FreeStyle Lite
        - Precision Xtra

    - NF and non-step preferred:
        - ACCU-CHEK Aviva Plus
        - GLUCOCARD 01-SENSOR
        - GLUCOCARD Vital
        - CONTOUR NEXT
        - FreeStyle InsuLinx
        - Nova Max
        - TRUEtest
        - Prodigy No Coding
        - OneTouch Verio
        - OneTouch Ultra Blue
        - All other test strips listed in Appendix D with the exception of FreeStyle Lite and Precision Xtra

    - This recommendation includes step therapy, which requires a trial of FreeStyle Lite or Precision Xtra prior to use of a NF test strip. The recommendation requires all current and new users of a non-preferred test strip try FreeStyle Lite or Precision Xtra, or meet the PA criteria for the non-preferred strips.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) maintaining Precision Xtra test strips on the BCF and adding FreeStyle Lite test strips to the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for the SMBGS test strips. See Appendix B for full criteria.

4. ***COMMITTEE ACTION: MANUAL PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) manual PA criteria for all new and current users of NF test strips. The manual PA criteria requires a trial of FreeStyle Lite or Precision Xtra prior to the use of a NF test strip. See Appendix C for the full criteria.

5. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) QLs for the SMBGS test strips, limiting use to 100 strips per 30-day supply in the Retail Network and 300 strips per 90-day supply in the Mail Order and MTF points of service. See Appendix F for the full criteria.

   Quantity Limits for the SMBGS test strips may be exceeded in the following situations: patient is receiving insulin; using an insulin pump; has gestational diabetes; requires more frequent testing due to endocrine disorders (e.g., insulinoma, endogenous hyperinsulinism, non-islet cell tumor); or, has a history of poorly controlled blood glucose levels with adverse outcomes (e.g., ketoacidosis or hypoglycemic episode), requiring medical intervention.

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 120-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is June 3, 2015.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: implement in 180 days.

B. Multiple Sclerosis (MS)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the MS Drug Class, which is comprised of the following injectable and oral disease-modifying drugs:

- **Injectable:** Interferon beta-1b (Betaseron and Extavia subcutaneous (SC) injections), interferon beta-1a (Avonex intramuscular (IM) injection; Rebif SC injection), and, glatiramer (Copaxone 20 mg SC daily injection and 40 mg three times a week (TIW) SC injection)

- **Oral**: dimethyl fumarate (Tecfidera), fingolimod (Gilenya), and teriflunomide (Aubagio)

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) the following conclusions for the MS drugs:

1. For the injectables, no one interferon product is preferred over the other in terms of efficacy and safety. Interferon beta-1a IM (Avonex) is possibly less effective than the other interferons, based on the Oregon Drug Effectiveness Review Project (DERP, 2010).
2. In a Cochrane review (2014), similar outcomes (including clinical and magnetic resonance imaging activity measures) were reported when the interferons were compared to glatiramer (Copaxone) for treating patients with relapsing-remitting forms of MS. These findings differ from the DERP 2010 report, where Avonex was presented as less effective.
3. The Copaxone 40 mg TIW formulation has the convenience of less frequent administration than the 20 mg daily Copaxone formulation. However, the 40 mg TIW product has not been directly compared to the 20 mg daily formulation for efficacy or safety; trials are ongoing.
4. There are no head-to-head trials of one oral drug with another oral drug; placebo controlled studies were used to obtain FDA approval. Limited data from head-to-head trials of the injectables versus oral medications report the following:
    - Fingolimod produces a greater reduction in the annualized relapse rate (ARR) compared to interferon beta-1a IM (Avonex).
    - Teriflunomide (Aubagio) 14 mg and interferon beta-1a SC (Rebif) produced similar reductions in the ARR, while teriflunomide 7 mg was less effective than the 14 mg dose and Rebif.
    - There were no clinically relevant differences in the ARR when glatiramer (Copaxone) was compared to dimethyl fumarate (Tecfidera).
5. The Canadian Agency for Drugs in Technology and Health (CADTH, October 2013) reported the relative ARRs of the various MS treatments compared to placebo. Fingolimod (Gilenya) and dimethyl fumarate (Tecfidera) had the lowest ARRs; teriflunomide, interferon beta-1b SC (Betaseron), interferon beta-1a SC (Rebif), and glatiramer (Copaxone) all had similar ARRs; and, interferon beta-1a (Avonex) had the highest ARR.
6. The MS drugs have distinctly different adverse event profiles. Copaxone has the advantage of a pregnancy category B rating.
7. Dalfampridine (Ampyra) is an orally administered drug that is not disease-modifying; it is solely approved for symptom management to improve walking distance.

8. Due to their differing safety profiles and low degree of therapeutic interchangeability, several MS products are required on the UF to meet the needs of the MHS population.

Relative Cost-Effectiveness Analysis and Conclusion—A cost-effectiveness analysis (CEA) and BIA were performed to evaluate the MS Drug Class. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- CEA results showed that, when considering the incremental cost-effectiveness ratios per relapse avoided, all scenarios were within a range considered to be cost-effective to the MHS. Ampyra was not included in the CEA as it is not a disease-modifying drug.
- BIA was performed to evaluate the potential impact of designating selected agents as formulary or NF on the UF. BIA results showed that all modeled scenarios demonstrated a similar level of cost avoidance for the MHS, with only slight differences between evaluated scenarios.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following:
    - UF:
        - Interferon beta-1a SQ (Rebif and Rebif Rebidose)
        - Interferon beta-1a IM (Avonex IM)
        - Interferon beta-1b SC (Betaseron)
        - Interferon beta-1b SC (Extavia)
        - Dalfampridine (Ampyra)
        - Dimethyl fumarate (Tecfidera)
        - Fingolimod (Gilenya)
        - Glatiramer (Copaxone)
        - Teriflunomide (Aubagio)
    - NF: None
2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The MS Drugs Class is now a BCF class; it was previously an Extended Core Formulary (ECF) drug class. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) interferon beta-1b SC (Betaseron) be designated with BCF status since it is the most cost-effective MS drug. As a result of this action, interferon beta-1a IM (Avonex) is no longer ECF; it remains on the UF.
3. ***COMMITTEE ACTION: MANUAL PA CRITERIA***—Manual PA criteria recommended in November 2010 and November 2013 currently apply to fingolimod (Gilenya) and dimethyl fumarate (Tecfidera), respectively. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) maintaining the current PA criteria for Tecfidera and

revising the PA criteria for Gilenya due to recent updates in the package insert for cardiovascular toxicity. See Appendix C for full criteria.

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date no later than 30 days after signing of the minutes in all POS.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. Prior Authorizations and Medical Necessity

1. **Hepatitis C Virus (HCV) Agents, Direct Acting Antivirals (DAAs): Ledipasvir/Sofosbuvir (Harvoni) Manual PA Criteria and QLs**—Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) is a once daily fixed dose combination tablet that was approved by the FDA in October 2014 for the treatment of HCV genotype 1. It is the first FDA-approved interferon-free regimen indicated to treat HCV genotype 1. Harvoni will be reviewed as a new drug at an upcoming meeting.

   a) ***COMMITTEE ACTION: HARVONI MANUAL PA CRITERIA***—PA criteria currently apply to the DAAs. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users of ledipasvir/sofosbuvir (Harvoni), consistent with FDA-approved labeling. Prior authorization will expire after 8–24 weeks based on the treatment regimen. See Appendix E for the full criteria.

2. **Hepatitis C Virus Agents, Direct Acting Antivirals (DAAs): Simeprevir (Olysio) Manual PA Criteria**—PA criteria were recommended for Simeprevir (Olysio) at the May 2014 DoD P&T Committee meeting. Simeprevir received a new FDA indication in November 2014 as a component of an interferon-free combination treatment for chronic HCV genotype 1.

   a) ***COMMITTEE ACTION: SIMEPREVIR (OLYSIO) PA CRITERIA***
   The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) revising the existing PA criteria for Olysio to include the expanded FDA-approved indication. See Appendix E for the full criteria.

3. **Targeted Immunomodulatory Biologics (TIBs): Adalimumab (Humira), Apremilast (Otezla), and Etanercept (Enbrel)**—The TIBs were reviewed by the P&T Committee in August 2014 and automated PA (step therapy) and manual PA criteria

were recommended for the class. Recently, adalimumab (Humira) received FDA approval for pediatric Crohn's disease in patients as young as six years and juvenile idiopathic arthritis (JIA) in patients as young as four years; apremilast (Otezla) received FDA approval for plaque psoriasis. PA criteria were updated for Humira and Otezla to reflect their new respective FDA indications. See Appendix C for the full criteria.

Accordingly, step therapy criteria and MN criteria for etanercept (Enbrel) were also revised since Enbrel and Humira are now indicated for the same age range in patients with JIA.

a) ***COMMITTEE ACTION: ADALIMUMAB (HUMIRA) AND APREMILAST (OTEZLA) PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) revised manual and step therapy PA criteria for Humira and Otezla, consistent with the new FDA-approved product labeling. See Appendix C for the full criteria.

b) ***COMMITTEE ACTION: ETANERCEPT (ENBREL) MN AND PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) an update to the MN and PA criteria for Enbrel since Humira is now indicated for JIA. See Appendices B and C for the full criteria.

4. **Prostate Cancer: Enzalutamide (Xtandi)**—Xtandi is an androgen receptor inhibitor that prolongs survival of metastatic castration-resistant prostate cancer. Manual PA criteria were recommended at the November 2012 P&T Committee meeting. The package insert for Xtandi was updated to state that prior treatment with docetaxel is no longer required.

a) ***COMMITTEE ACTION: ENZALUTAMIDE (XTANDI) PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) an update to the manual PA criteria for Xtandi, consistent with the product's labeling for treatment of metastatic castration-resistant prostate cancer. See Appendix C for the full criteria.

5. **Non-Insulin Diabetes Mellitus Drugs: Glucagon-Like Peptide-1 Receptor Agonist (GLP1RAs); Exenatide Once Weekly Pen (Bydureon Pen)**—Exenatide (Bydureon) is now available in a pre-filled pen, in addition to the original vial formulation. The manufacturer states that they do not intend to discontinue the original vial formulation. Both products are dosed once weekly. However, the cost of the Bydureon pen formulation is significantly higher than the Bydureon vials despite having the same dosing and FDA-approved indications. Exenatide (Byetta) is also available in a pen formulation that is dosed twice daily. Manual PA criteria were recommended for the Bydureon pen due to the cost and because other exenatide products (Bydureon vials and Byetta) are available on the UF. The GLP1RA Drug Subclass, including the Bydureon

pen formulation, is scheduled for review at an upcoming meeting.

a) ***COMMITTEE ACTION: EXENATIDE PEN (BYDUREON PEN) PA CRITERIA***—The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 1 absent) manual PA criteria for the Bydureon pen, requiring use of Bydureon vials first. Additionally, a trial of metformin or a sulfonylurea is also required, consistent with the PA criteria for other GLP1RAs. See Appendix C for the full criteria.

B. QLs—QLs for several drugs were reviewed, including the HCV direct acting antiviral ledipasvir/sofosbuvir (Harvoni); the pulmonary fibrosis drugs nintedanib (Ofev) and pirfenidone (Esbriet); and, the LABA olodaterol (Striverdi Respimat). QLs apply to the other products in these drug classes.

1. ***COMMITTEE ACTIONS: QLs***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) QLs for ledipasvir/sofosbuvir (Harvoni), nintedanib (Ofev), pirfenidone (Esbriet), and olodaterol (Striverdi Respimat), consistent with the product labeling. See Appendix F for QLs.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

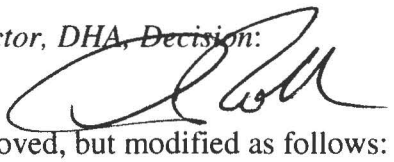
VII. SECTION 716 OF THE NATIONAL DEFENSE AUTHORIZATION ACT (NDAA) FISCAL YEAR 2013 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM

A. Medication Drug List for the Pilot Program: Updates—The Medication Drug list for the Pilot Program for TRICARE for Life beneficiaries was recommended at the November 2013 P&T Committee meeting. An update to the drug list is required due to products discontinuations from the market, availability issues, and to ensure consistency within the drug classes. See the TRICARE Formulary Search Tool at *http://pec.ha.osd.mil/TFL_maintenance_drug_list.php* for the full medication drug list.

1. ***COMMITTEE ACTION: MAINTENANCE MEDICATION PROGRAM DRUG LIST UPDATE***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) changes to the list of covered maintenance medications for the Section 716 pilot program. Implementation will occur upon signing of the minutes. See Appendix H for the full list of changes.

☑ Approved ☐ Disapproved

Director, DHA, Decision:



Approved, but modified as follows:

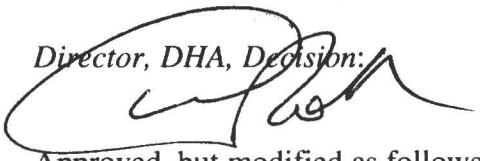
VIII. LINE EXTENSIONS

A. Formulary Status Clarification—The P&T Committee clarified the formulary status for one product line extension ("follow-on product") by the original manufacturer. Line extensions have the same FDA indications and pricing as the "parent" drug.

1. ***COMMITTEE ACTION: LINE EXTENSIONS FORMULARY STATUS CLARIFICATION***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) clarifying the formulary status of insulin detemir (Levemir Flextouch). The Levemir Flextouch formulation is replacing the Levemir Flexpen formulation, which was discontinued from the market in the summer of 2014. Implementation will occur upon signing of the minutes.

    - Insulin detemir (Levemir Flextouch): NF, similar to Levemir Flexpen

Director, DHA, Decision: ☑ Approved ☐ Disapproved



Approved, but modified as follows:

IX. COMPOUND PRESCRIPTIONS

A. PA Criteria—The P&T Committee was presented with an update on the status of compounded medications. MHS expenditures for compounded medications are significant and increasing, and compounded medications have a high potential for inappropriate use. From June 2013 through May 2014, 140,000 beneficiaries filled 360,000 compounded prescriptions that totaled over $410 million in expenditures at the Retail Network and Mail Order POS. In an effort to decrease inappropriate use and ensure safety for beneficiaries, PA criteria were proposed.

1. ***COMMITTEE ACTION: COMPOUND PRESCRIPTIONS MANUAL PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) manual PA criteria for all new and current users of compounds. Coverage will be approved if the prescriber provides the following information listed below and implementation of the PA will occur when a final recommendation is made.

    a) What is the diagnosis?

b) Has the patient tried commercially available products for the diagnosis provided? Please state all products tried.

c) Is there a current national drug shortage of an otherwise commercially available product?

d) What is the proposed duration of therapy?

AND

The patient meets the following criteria:

(1) Each active ingredient(s) is/are a chemical entity of an FDA-approved drug for marketing in the United States AND the drugs have not been withdrawn for safety reasons from the U.S. market. (If True, proceed to (2); if False, claim rejects.)

(2) Each active ingredient(s) used in this compound is indicated by the FDA to treat the diagnosis provided. (If True, proceed to (3); if False, claim rejects.)

(3) An FDA-approved commercially available product is not appropriate because the patient requires a unique dosage form or concentration (e.g., inability to take a solid dosage form, dose based on age or weight) and/or an FDA-approved product cannot be taken due to allergies or contraindication. (If True, Approved; if False, claim rejects.

Director, DHA, Decision: □ Approved ☒ Disapproved

Approved, but modified as follows: pending consideration of BAP recommendations

X. SPECIALTY MEDICATIONS

A. Clinical Services Drug List and DoD Specialty Agent Reporting List—The P&T Committee was briefed on two separate drug lists for specialty medications, the Clinical Services Drug List and the DoD Specialty Agent Reporting List.

Drugs are assigned to the DoD Specialty Agent Reporting List when they generally meet at least two of these four criteria: cost $500 or more per dose or $6,000 or more per year, have a difficult or unusual process of delivery, require patient management beyond traditional dispensing practices, or as defined by DoD. The DoD Specialty Agent Reporting List is used internally for reporting purposes to monitor drug spend and trends in utilization of specialty medications.

The Clinical Services Drug List is a subset of the DoD Specialty Agent Reporting List and identifies drugs for which contractor-provided pharmacy services at the Retail Network and Mail Order Pharmacy will be provided in conjunction with the new TRICARE Pharmacy contract effective in May 2015.

The P&T Committee reviewed the list of drugs recommended for the Clinical Services Drugs List and voted to remove drugs that are no longer marketed, remove drugs that do not require enhanced clinical services, remove certain drugs classes to allow consideration at future P&T Committee meetings, and add drugs to the list that meet the definition above and require enhanced clinical services.

The Clinical Services Drug List comprises 79 products from a variety of drug classes, including bleeding disorders (hemophilia), MS, HCV, rheumatoid arthritis and other inflammatory conditions, oncology, osteoporosis, neutropenia, acromegaly, iron overload, and hormonal therapies.

The P&T Committee also recommended that additions or deletions to the Clinical Services Drug List be made administratively when new products are approved or when market discontinuations occur to maintain the currency of the list and to ensure timely patient access to specialty medications. The P&T Committee will then review any administrative actions at the next scheduled P&T Committee meeting.

1. ***COMMITTEE ACTION: CLINICAL SERVICES DRUG LIST AND DOD SPECIALTY AGENT REPORTING LIST***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the changes to the Clinical Services Drug List outlined above, and recommended the List be maintained administratively, with any additions or deletions reported at the next scheduled DoD P&T Committee meeting.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

XI. ITEMS FOR INFORMATION

A. Naloxone—The P&T Committee was briefed on an executive action by President Obama to expand the availability of opioid overdose reversal kits for first responders on military bases and other areas under DoD control to improve patient safety and prevent suicides. In April 2014, the FDA approved the first naloxone auto-injectable (Evzio) formulation intended for caregiver administration in emergency situations. The potential implications of wider access of Evzio to patients/family members using opioids who are at increased risk for opioid overdose were discussed. Updates to the P&T Committee will be provided as new information becomes available.

B. UF Proposed Rule—A Proposed Pharmacy TRICARE Rule published in the CFR on September 19, 2014 (http://www.gpo.gov/fdsys/pkg/FR-2014-09-19/pdf/2014-22276.pdf) proposes administrative changes to align the Pharmacy Benefit Program regulation with the statute (10 U.S.C. 1074g), clarifies some uniform formulary procedures, and designates the over-the-counter demonstration program as permanent. The main points of the Proposed Rule are to limit NF drugs to one point of service, place new drugs approved by the FDA in a provisional status for 120 days, and allow generic drugs to be placed in the third tier co-pay. The review period is scheduled to end on January 19, 2015.

XII. ADJOURNMENT

The meeting adjourned at 1130 hours on November 20, 2014. The next meeting will be in February 2015.

Appendix A—Attendance: November 2014 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Self-Monitoring Blood Glucose System Test Strips

Appendix E—Table of Prior Authorization Criteria for Hepatitis C Drugs

Appendix F—Table of Quantity Limits

Appendix G—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix H—Section 716 Maintenance Medication Program Drug List

Appendix I—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

3 Feb 2015
Date

Appendix A—Attendance: November 2014 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
George Jones, PharmD, M.S.	Chief, DHA Pharmacy Operations Division
LTC Robert Conrad, MS	DHA Pharmacy Operations Division (Recorder)
COL John Spain, MS	Army, Pharmacy Officer
Col Scott Sprenger, BSC	Air Force, Pharmacy Officer
CDR Aaron Middlekauf, USCG	Coast Guard, Pharmacy Officer Alternate
CAPT Thinh Ha, MSC	Navy, Pharmacy Officer
COL Ted Cieslak, MC	Army, Physician at Large
Col Michael Wynn, MC	Army, Family Practice Physician
LCDR Carey Welsh, MC	Navy, Pediatrics Physician
Col James Jablonski, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Larissa Weir, MC	Air Force, OB/GYN Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Voting Members Absent	
Col Michael Spilker, BSC	DHA Deputy Chief, Pharmacy Operations Division
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. Paul Hutter	Principal Deputy General Counsel, DHA
Mr. Bryan Wheeler via DCO	Deputy General Counsel, DHA
Guests	
Mr. Bill Davies via DCO	DHA Pharmacy Operations Division
MAJ Kevin Ridderhoff	DHA, Pharmacy Operations Division
CDR Ryan Schupbach	Indian Health Service
LT Kendra Jenkins via DCO	DHA, Pharmacy Operations Division

Appendix A—Attendance (continued)

Others Present	
CAPT Walter Downs, MC	DHA Pharmacy Operations Division
CDR Joshua Devine, USPHS	DHA Pharmacy Operations Division
CDR Edward Vonberg, BSC	DHA Pharmacy Operations Division
LTC Misty Cowan, MC	DHA Pharmacy Operations Division
LCDR Marisol Martinez, USPHS	DHA Pharmacy Operations Division
Maj David Folmar, BSC	DHA Pharmacy Operations Division
Maj Ronald Khoury, MC	DHA Pharmacy Operations Division
Angela Allerman, PharmD, BCPS	DHA Pharmacy Operations Division
Shana Trice, PharmD, BCPS	DHA Pharmacy Operations Division
Amy Lugo, PharmD, BCPS via DCO	DHA Pharmacy Operations Division
Eugene Moore, PharmD, BCPS	DHA Pharmacy Operations Division
Brian Beck, PharmD, BCPS	DHA Pharmacy Operations Division
David Meade, PharmD, BCPS	DHA Pharmacy Operations Division
Ms. Deborah Garcia	DHA Pharmacy Operations Division contractor
Mr. Kirk Stocker	DHA Pharmacy Operations Division contractor
Esmond Nwokeji, PhD	DHA Pharmacy Operations Division contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Valeritas Insulin Delivery Device (V-Go) **Insulin–Miscellaneous Insulin Delivery Devices**	• Formulary agents result or are likely to result in therapeutic failure **Formulary alternative:** Uniform Formulary insulin products (insulin glargine, insulin lispro, insulin aspart) pens and vials
• Bromfenac 0.07% ophthalmic solution (Prolensa) **Ophthalmic NSAIDS**	• Patient has experienced or is likely to experience significant adverse effects from formulary agents **Formulary alternatives:** bromfenac, diclofenac, flurbiprofen, ketorolac, nepafenac ophthalmic NSAIDs
• ACCU-CHEK Aviva Plus • GLUCOCARD 01-SENSOR • GLUCOCARD Vital • CONTOUR NEXT • FreeStyle InsuLinx • Nova Max • TRUEtest • Prodigy No Coding • One Touch Verio • One Touch Ultra Blue • Plus all other SMBGS test strips listed in Appendix D, except for FreeStyle Lite and Precision Xtra **Self-Monitoring Blood Glucose System (SMBGS) test strips**	• No alternative formulary – applies in the following situations: • Patient is blind/severely visually impaired and requires a test strip used in a talking meter – Prodigy Voice, Prodigy AutoCode, Advocate Redicode • Patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter o Contour NEXT strip with CONTOUR NEXT Link meter for Medtronic pump o Nova Max strip with Nova Max Link meter for Medtronic pump o For Retail Network Only: One Touch Ultra test strips with One Touch Ultra Link meter for Medtronic Mini Med Paradigm insulin pump o For Retail Network Only: One Touch Ultra test strips with One Touch Ping meter and using the One Touch Ping insulin pump • The patient has a documented physical or mental health disability requiring a special strip or meter. For example, the patient requires ACCU-CHEK Aviva Plus strip due to manual dexterity issues (Arthritis Association Seal of Approval) **Formulary alternatives:** Freestyle Lite and Precision Xtra
• Etanercept (Enbrel) **Targeted Immunomodulatory Biologics (TIBs)**	• Use of adalimumab (Humira) is contraindicated • The patient has experienced or is likely to experience significant adverse effects from adalimumab (Humira) • Adalimumab (Humira) resulted or is likely to result in therapeutic failure. • The patient previously responded to the nonformulary agent and changing to adalimumab (Humira) would incur unacceptable risk • No alternative formulary agent applies only to: 1. Abatacept (Orencia): The patient is transitioning from IV abatacept or has symptomatic congestive heart failure (CHF). 2. Anakinra (Kineret): The patient has neonatal onset multisystem inflammatory disease (NOMID), a subtype of cryopyrin associated periodic syndrome (CAPS). 3. Etanercept (Enbrel): The patient has hepatitis C infection. 4. Tocilizumab (Actemra): The patient is transitioning from IV abatacept or has symptomatic CHF. **Formulary alternative: adalimumab (Humira)**

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Valeritas Insulin Delivery Device (V-Go) **Insulin–Miscellaneous Insulin Delivery Devices**	PA criteria apply to all new users of the V-Go device. Manual PA criteria: (1) Patient has Type 2 diabetes mellitus (2) Patient does not need more than 40 units of basal insulin daily AND the patient does not need more than 36 units of bolus insulin daily (3) Patient does not need less than 2 unit increments of bolus dosing (4) Patient has been maintained on stable basal insulin for at least 3 months (at dosages ranging from 20U to 40U) (5) Patient has been using prandial insulin for at least 3 months
• Fingolimod (Gilenya) **Multiple Sclerosis Drugs (MS)**	Manual PA criteria: • A documented diagnosis of relapsing forms of MS • No current use of a disease-modifying therapy (e.g., interferon 1a or 1b or Copaxone) • Avoid use in patients with significant cardiac history, including: o Patients with a recent history (within the past 6 months) of class III/IV heart failure, myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization o Those with a history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless they have a functioning pacemaker o Patients with a baseline QTc interval ≥500 ms o Those receiving treatment with class Ia or class III antiarrhythmic drugs
• ACCU-CHEK Aviva Plus • GLUCOCARD 01-SENSOR • GLUCOCARD Vital • CONTOUR NEXT • FreeStyle InsuLinx • Nova Max • TRUEtest • Prodigy No Coding • One Touch Verio • One Touch Ultra Blue • Plus all other SMBGS test strips listed in Appendix D **Self-Monitoring Blood Glucose System (SMBGS) test strips**	New and current users of the nonformulary test strips are required to try FreeStyle Lite or Precision Xtra Manual PA Criteria—Non-preferred test strip allowed if: • Patient is blind/severely visually impaired and requires a test strip used in a talking meter – Prodigy Voice, Prodigy AutoCode, Advocate Redicode • Patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter o Contour NEXT strip with CONTOUR NEXT Link meter for Medtronic pump o Nova Max strip with Nova Max Link meter for Medtronic pump o For Retail Network Only: One Touch Ultra test strips with One Touch Ultra Link meter for Medtronic Mini Med Paradigm insulin pump o For Retail Network Only: One Touch Ultra test strips with One Touch Ping meter and using the One Touch Ping insulin pump • The patient has a documented physical or mental health disability requiring a special strip or meter. For example, the patient requires ACCU-CHEK Aviva Plus strip due to manual dexterity issues (Arthritis Association Seal of Approval)
• Adalimumab (Humira) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: (Changes highlighted in bold) • Moderate to severe active rheumatoid arthritis, active psoriatic arthritis, or active ankylosing spondylitis • Moderate to severe chronic plaque psoriasis who are candidates for systemic or phototherapy, and when other systemic therapies are medically

Drug / Drug Class	Prior Authorization Criteria
• Adalimumab (Humira) **Targeted Immunomodulatory Biologics (TIBs)**	less appropriate • Moderate to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to Remicade, or an inability to tolerate Remicade • Moderate to severely active ulcerative colitis following inadequate response to immunosuppressants **Pediatric patients with** • **Moderate to severe active polyarticular juvenile idiopathic arthritis (pediatric patients: 2–17 years)** • **Moderate to severely active Crohn's disease (≥ 6 years)** who have had an inadequate response to corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate Coverage is NOT provided for concomitant use with other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Apremilast (Otezla) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Otezla if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF • Adverse reactions to Humira not expected with requested non-step preferred TIB AND Coverage approved for patients ≥ 18 years with: • Active psoriatic arthritis • **Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy** Coverage is NOT provided for concomitant use with other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Etanercept (Enbrel) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Enbrel if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF)

Drug / Drug Class	Prior Authorization Criteria
• Etanercept (Enbrel) **Targeted Immunomodulatory Biologics (TIBs)**	• Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative (Enbrel is prescribed for a patient with hepatitis C virus) AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis, active psoriatic arthritis, or active ankylosing spondylitis • Moderate to severe chronic plaque psoriasis who are candidates for systemic or phototherapy Coverage approved for pediatric patients (age 2–17) with: • Moderate to severe active polyarticular Juvenile Idiopathic Arthritis Coverage is NOT provided for concomitant use with other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Enzalutamide (Xtandi) **Prostate Cancer Drugs**	Coverage is approved if: • Documented diagnosis of metastatic castration-resistant prostate cancer No expiration date for the PA
• Exenatide once weekly pen (Bydureon pen) **Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)**	New GLP1RA users are required to try metformin or a sulfonylurea (SU) before receiving Byetta, Bydureon, or Victoza. Automated PA criteria: The patient has received a prescription for metformin or SU at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days, AND Manual PA criteria, if automated criteria are not met: Byetta, Bydureon, or Victoza is approved (e.g., trial of metformin or SU is NOT required) if: 1) The patient has a confirmed diagnosis of Type 2 Diabetes Mellitus 2) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis. 3) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment. 4) The patient has a contraindication to both metformin and a SU. 5) The patient has had an inadequate response to metformin and a SU. 6) **Also for exenatide once weekly (Bydureon pen)** ▪ **Coverage approved if patient has first tried Bydureon 2mg vial/cartridge first AND** ▪ **Patient has dexterity issues and cannot assemble the Bydureon vial/cartridge**

Appendix D—Table of Self-Monitoring Blood Glucose System Test Strips in the Class

FreeStyle Lite	Easy Touch	Reveal test strip
Precision Xtra	Easy Touch glucose	Relion Confirm Micro
ACCU-CHEK Aviva Plus	Easy Gluco	Relion Prime
GLUCOCARD 01-SENSOR	Easy Gluco G2 test strip	Rightest GS100 test strips
GLUCOCARD Vital	Element test strips	Rightest GS 300 test strips
CONTOUR NEXT	Element Plus	Rightest GS 550 test strips
FreeStyle Insulinx	Embrace	SmartDiabetes Xpres
Nova Max	Evencare test strip	Smartest test
TRUEtest	Evencare G2	Surechek test strips
Prodigy No Coding	EZ Smart	Surestep
OneTouch Verio	EZ Smart Plus Fast Take	Surestep Pro
OneTouch Ultra Blue	Fifty50 test strip	Sure test
ACCU-CHEK	Fora G20	Solus v2
ACCU-CHEK Active	Fora test strip	Telcare test strips
ACCU-CHEK Advantage	Fora v10	Tracer BG
ACCU-CHEK Aviva	Fora V12	TRUEtrack
ACCU-CHEK Comfort Curve	Fora V30a	TRUEtrack Smart System
ACCU-CHEK Instant	G-4 test strip	Ultima
ACCU-CHEK Smartview	GE blood glucose test	Ultratrak
AccuTrend glucose	GE100 blood glucose test strip	Ultratrak Pro
Acura test strips	GLUCOCARD Expression	Ultratrak Ultimate test strip
Advance test strips	GLUCOCARD X sensor	Victory
Advocate test strip	Glucolab	Wavesense AMP
Advocate Redi-Code	Glucose test strip	Wavesense Jazz
Advocate Redi-Code+	Glucometer Encore	Wavesense Presto
Ascensia Elite	Glucostix	
Assure 3	Infinity	
Assure 4	Keynote	
Assure Platinum	Liberty test strips	
Assure Pro	Micro	
BD test strips	Microdot	
BG-star	Neutek 2Tek test strips	
Blood glucose test strips	On Call Vivid test strip	
Blood glucose test strips – Leader	Optium	
Chemstrip BG	Optium EZ	
ChoiceDM G20	Pocketchem EZ	
ChoiceDM GD20	Precision PCX	
Clever Check	Precision PCX Plus	
Clever Choice test strips	Precision Point Of Care	
Clever Choice Pro	Precision QID	
Contour	Premium blood glucose	
Control	Prestige test	
Dextrostix reagent	Prestige smart system	
Easymax	Prodigy	
EasyPlus glucose test strips	Quintet	
EasyPlus mini strip	Quintet AC	
Easy Pro Plus	RefuAH Plus test strip	

Appendix E—Table of Prior Authorization (PA) Criteria for Hepatitis C Drugs

Prior Authorization Criteria

Ledipasvir/sofosbuvir (Harvoni)
Direct Acting Antiviral Subclass

- New users of ledipasvir/sofosbuvir (Harvoni) are required to undergo the PA process.
- Current users are not affected by PA; they can continue therapy uninterrupted.
- Patients are encouraged to use the Mail Order Pharmacy or MTFs to fill their Harvoni prescriptions.
- Consult the AASLD/IDSA HCV guidelines (www.hcvguidelines.org) for the most up-to-date and comprehensive treatment for HCV. Unique patient populations are also addressed, and treatment recommendations may differ from those for the general population.

Manual PA Criteria:

- Age ≥ 18
- Has laboratory evidence of chronic HCV genotype 1 infection
    1. State the HCV genotype and HCV RNA viral load on the PA form
- Ledipasvir/sofosbuvir (Harvoni) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.
- The patient is not co-infected with Hepatitis B virus (HBV).

Treatment Regimens and Duration of Therapy

- Treatment and duration of therapy are approved for one of the following regimens outlined below, based on HCV genotype, prior treatment, and presence of cirrhosis.
- Prior authorization will expire after 8 weeks or 12 weeks or 24 weeks, based on the treatment regimen selected.

Genotype 1 Patient Populations	***Treatment Duration***
Treatment naïve with or without cirrhosis	8* - 12 weeks
Treatment experienced** without cirrhosis	12 weeks
Treatment experienced** with cirrhosis	24 weeks
*Consider treatment duration of 8 weeks in treatment-naïve patients without cirrhosis who have a pretreatment HCV RNA less than 6 million IU/mL. **Treatment-experienced patients who have failed treatment with either (a) peginterferon alfa plus ribavirin or (b) HCV protease inhibitor plus peginterferon alfa plus ribavirin	

Prior Authorization Criteria

Simeprevir (Olysio)
Direct Acting Antiviral Subclass

- New users of simeprevir (Olysio) are required to undergo the PA process.
- Current users are not affected by PA; they can continue therapy uninterrupted.
- The FDA-approved indication of simeprevir + PEG-interferon + ribavirin for 24 to 48 weeks is not recommended for HCV treatment by the AASLD/IDSA. See www.hcvguidelines.org.
- Patients are encouraged to use the Mail Order Pharmacy or MTFs to fill their simeprevir prescriptions.
- Consult the AASLD/IDSA HCV guidelines (www.hcvguidelines.org) for the most up-to-date and comprehensive treatment for HCV. Unique patient populations are also addressed, and treatment recommendations may differ from those for the general population.

Manual PA Criteria:

- Age ≥ 18
- Has laboratory evidence of chronic HCV genotype 1 infection
- State the HCV genotype and HCV RNA viral load on the PA form
- If HCV genotype 1a, the patient is negative for NS3 Q80K polymorphism at baseline
- Simeprevir (Olysio) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.
- The patient is not co-infected with HIV or Hepatitis B virus (HBV).
- Not recommended for monotherapy
- The patient has not previously used a HCV protease inhibitor (boceprevir, telaprevir, or simeprevir)

Treatment Regimens and Duration of Therapy

- Treatment and duration of therapy are approved for one of the following regimens outlined below, based on HCV genotype, prior treatment, and presence of cirrhosis.
- Prior authorization will expire after 12 weeks or 24 weeks, based on the treatment regimen selected.

Genotype 1 Patient Populations	Treatments	Treatment Duration
Treatment naïve or experienced* without cirrhosis	simeprevir 150 mg once daily sofosbuvir 400 mg once daily	12 weeks
Treatment naïve or experienced* with cirrhosis	simeprevir 150 mg once daily sofosbuvir 400 mg once daily	24 weeks
*Treatment-experienced patients who have failed treatment with peginterferon alfa plus ribavirin but not a HCV protease inhibitor Prior Authorization expires at the end of treatment duration (12–24 weeks)		

Appendix F—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
Self-Monitoring Blood Glucose Test Strips (all products)	▪ Retail Network: 100 strips/30-day supply ▪ Mail Order and MTF: 300 strips/90-day supply Override criteria include the following situations: ▪ receiving insulin ▪ using an insulin pump ▪ gestational diabetes ▪ requires more frequent testing due to endocrine disorders (e.g., insulinoma, endogenous hyperinsulinism, non-islet cell tumor) ▪ history of poorly-controlled blood glucose levels with history of adverse outcomes (e.g., ketoacidosis or hypoglycemic episode) requiring medical intervention
• Umeclidinium/vilanterol (Anoro Ellipta) **Pulmonary II Drugs for COPD**	▪ Retail Network: 1 inhaler per 30 days ▪ Mail Order and MTF: 3 inhalers per 90 days
• Ledipasvir/sofosbuvir (Harvoni **Hepatitis C Drugs–Direct Acting Agents**	▪ Retail Network, Mail Order and MTF: 28 tablets per 28 days
• Nintedanib (Ofev) **Pulmonary Fibrosis**	▪ Retail Network, Mail Order, and MTF: 50/100 mg capsules, 60 tabs (30-day supply)
• Pirfenidone (Esbriet) **Pulmonary Fibrosis**	▪ Retail Network, Mail Order, and MTF: 267 mg caps, 270 capsules (30-day supply)
• Olodaterol (Striverdi Respimat) **Pulmonary Fibrosis Long-Acting Beta Agonist (LABA)**	▪ Retail Network: 1 inhaler (60 actuations) per 30 days ▪ Mail Order and MTF: 3 inhalers (180 actuations) per 90 days

Appendix G—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2014	**Multiple Sclerosis Drugs**	UF class review Previously reviewed	▪ Interferon beta-1b SC (Betaseron)	▪ Interferon beta-1a SC (Rebif and Rebif Rebidose) ▪ Interferon beta-1a IM (Avonex) ▪ Interferon beta 1b SC (Extavia) ▪ Dalfampridine (Ampyra) ▪ Teriflunomide (Aubagio) ▪ Glatiramer (Copaxone) ▪ Fingolimod (Gilenya) ▪ Dimethyl fumarate (Tecfidera)	▪ None	Pending singing of the minutes / 30 days	▪PA required for Gilenya and Tecfidera (See Appendix C)	▪ MS drugs s are no longer an ECF class; Betaseron is now BCF and Avonex is removed from the ECF.
Nov 2014	**Pulmonary II: Chronic Obstructive Pulmonary Disease**	New Drug Review	▪ Ipratropium bromide (Atrovent HFA) ▪ Ipratropium bromide/albuterol nebulized solution (Duoneb) ▪ Salmeterol (Serevent) ▪ Tiotropium (Spiriva)	**May 2013** ▪ Aclidinium (Tudorza) ▪ Arformoterol (Brovana) ▪ Formoterol (Foradil) ▪ Ipratropium bromide/albuterol (Combivent Respimat) ▪ Roflumilast (Daliresp) **Nov 2014** ▪ **Umeclidinium/ vilanterol (Anoro Ellipta) Nov 2014**	▪ Formoterol (Perforomist) ▪ Indacaterol (Arcapta)	Pending signing of the minutes	▪QL apply	▪ BCF, UF, and NF choices are designated for COPD drugs for LABAs, LAMAs, SABA/SAMA, SAMAs, and oral PDE-4 inhibitors. See DoD P&T Minutes for Feb 2009, May 2013, and May 2014.
Nov 2014	**Ophthalmic NSAIDs**	New Drug Review	▪ None	**Aug 2010** ▪ Bromfenac 0.9%, generic ▪ Diclofenac (Voltaren) ▪ Flurbiprofen (Ocufen) ▪ Ketorolac 0.4% (Acular LS) ▪ Ketorolac 0.45% (Acuvail) ▪ Ketorolac 0.5% (Acular) ▪ Nepafenac (Nevanac)	**Nov 2014** ▪ **Bromfenac 0.07% (Prolensa)**	Pending singing of the minutes / 90 days	▪None	▪ Medical Necessity Criteria apply. See Appendix B

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2014	**Ophthalmic Glaucoma Agents**	New Drug Review	▪ Latanoprost, generic ▪ Timolol, generic ▪ Brimonidine 0.15%, 0.2%, generic	**Nov 2014** ▪ **brinzolamide 1% /brimonidine 0.2% (Simbrinza)** **Feb 2007** ▪ Bimatoprost (Lumigan) ▪ Betaxolol (Betoptic, Betoptic-S) ▪ Carteolol (Ocupress) ▪ Levobunolol (Betagan) ▪ Metipranolol (Optipranolol) ▪ Timolol maleate (Timoptic) ▪ Timolol maleate gel forming solution (Timoptic XE) ▪ Dorzolamide (Trusopt) ▪ Dorzolamide / timolol (Cosopt) ▪ Brimonidine purite 0.1% (Alphagan P) ▪ Apraclonidine (Iopidine) ▪ Dipivefrin (Propine) ▪ Acetylcholine (Miochol-E) ▪ Carbachol (Isopto Carbachol) ▪ Pilocarpine (Pilocar, Pilopine HS) ▪ Echothiophate (Phospholine iodide)	▪ travoprost (Travatan and Travatan Z) ▪ tafluprost (Zioptan) ▪ timolol (Betimol) ▪ timolol (Istalol) ▪ brinzolamide (Azopt)	Pending singing of the minutes / 90 days	▪None	▪ None

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2014	**Self-Monitoring Blood Glucose System (SMBS) test strips**	UF Class Review	▪ FreeStyle Lite (Abbott) ▪ Precision Xtra (Abbott)	Uniform Formulary and Step-Preferred ▪ FreeStyle Lite (Abbott) ▪ Precision Xtra (Abbott)	Nonformulary and non-step preferred ▪ACCU-CHEK Aviva Plus (Roche) ▪GLUCOCARD 01-SENSOR (Arkray) ▪GLUCOCARD Vital (Arkray) ▪CONTOUR NEXT (Bayer) ▪ FreeStyle InsuLinx (Abbott) ▪NovaMax (Nova) ▪TRUEtest (Nipro) ▪Prodigy No Coding (Prodigy) ▪One Touch Ultra Blue (Lifescan) ▪One Touch Verio (Lifescan) ▪For a V2 (For a) ▪Solus V12 (Biosense) ▪All other test strips listed in Appendix D, with the exception of Freestyle Lite, and Precision Xtra	Pending signing of the minutes / 120 days	Step therapy requires a trial of an FreeStyle Lite, or Precision Xtra in all new and current users of the nonformulary strips	▪ FreeStyle Lite added to the BCF; Precision Xtra remains on the BCF

TRICARE Formulary Search tool: *http://www.pec.ha.osd.mil/formulary_search.php*

Appendix H—Section 716 Maintenance Medication Program Drug List

- Removed from list due to manufacturer discontinuation:
  - ANTARA 45 mg, 130 mg CAPS
  - CENESTIN 0.3, 0.45 mg TABS
  - LEVATOL 20 mg TABs
  - LUVOX CR 150 mg CAPS
  - SANCTURA 20 mg TABS
  - UNIRETIC 7.5 mg/12.5 mg TABS

- Added to the list, due to consistency with the drug class (new strengths or dosage formulations):
  - ACTONEL 30 mg TABLET
  - ANGELIQ 0.25 mg–0.5 mg TABLET
  - ARICEPT 23 mg TABLET
  - BETAPACE 160 mg TABLET
  - CARAFATE 1 g/10 ml ORAL SUSP
  - CLORPRES 0.1 mg–15 mg TABLET
  - EFFER-K 25 mEq TABLET EFF
  - EXELON 13.3 mg/24 hours PATCH TD24
  - KLOR-CON 20 mEq PACKET
  - K-TAB ER 20 mEq TABLET ER
  - LANOXIN 62.5 mcg and 1875 mcg TABLET
  - LUPRON DEPOT 45 mg SYRINGE KIT
  - LUPRON DEPOT-PED 30 mg and 11.25 mg SYRINGE KIT
  - MINITRAN 0.4 mg/hr PATCH TD24
  - NAPROSYN 250 mg TABLET
  - NEUPRO 1 mg/24 hour, 3 mg/24 hour and 8 mg/24 hour PATCH TD24
  - NEXIUM 2.5 mg and 5 mg SUSPDR PKT
  - NORDITROPIN FLEXPRO 10 mg/1.5 ml PEN
  - NUTROPIN AQ 20 mg/2 ml CARTRIDGE and NUTROPIN AQ NUSPIN 5 mg/2 ml CARTRIDGE
  - RAZADYNE ER 8 mg CAP 24 hour PEL
  - SAIZEN 8.8 mg VIAL and 8.8 mg/1.5 CARTRIDGE
  - SPRYCEL 140 mg TABLET
  - TRELSTAR 3.75 mg/2 ml SYRINGE
  - NAMENDA 5 mg–10 mg TAB DS PK

Appendix I—Table of Abbreviations

ARR	annualized relapse rate
BCF	Basic Core Formulary
BIA	budget impact analysis
CADHT	Canadian Agency for Drugs in Technology and Health
CEA	cost-effectiveness analysis
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DAAs	direct acting antivirals
DCO	Defense Connect Online
DERP	Oregon Drug Effectiveness Review Project
DHA	Defense Health Agency
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
FDA	U.S. Food and Drug Administration
FEV_1	forced expiration volume in 1 second
GLP1RA	glucagon-like peptide-1 receptor agonist
HCV	hepatitis C virus
IM	intramuscular
IOP	intraocular pressure
ISO	International Organization for Standardization
JIA	juvenile idiopathic arthritis
LABA	long-acting beta agonist
LAMA	long-acting muscarinic agent
MHS	Military Health System
MN	medical necessity
MS	multiple sclerosis
MTF	Military Treatment Facility
NF	nonformulary
NDAA	National Defense Authorization Act
NSAIDs	nonsteroidal anti-inflammatory drugs
P&T	Pharmacy and Therapeutics
PA	prior authorization
POS	points of service
QD	once daily
QLs	quantity limits
SC	subcutaneous
SMBGS	self-monitoring blood glucose system
TIBs	targeted immunomodulatory biologics
TIW	three times a week
UF	Uniform Formulary
V-Go	Valeritas V-Go insulin delivery device

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

August 2014

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 13, 2014, at the Defense Health Agency (DHA) Pharmacoeconomic Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May Minutes**—Lt. Gen. Douglas J. Robb, DO, MPH, Director, DHA, approved the minutes for the May 2014 DoD P&T Committee meeting on September 12, 2014.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Non-Insulin Diabetes Drugs—Glucagon-Like Peptide-1 Receptor Agonist (GLP1RA): Albiglutide (Tanzeum)

Background—Albiglutide (Tanzeum) is the fourth GLP1RA and the second product with once weekly dosing. Similar to the other GLP1RAs [(exenatide once weekly (Bydureon), liraglutide (Victoza), and exenatide twice daily (Byetta)], albiglutide has beneficial effects on reducing hemoglobin A1c, blood pressure, weight, and improving lipid lab profiles. Albiglutide has a lower incidence of nausea and vomiting compared to Bydureon, Victoza, or Byetta. However, it has a slightly higher incidence of diarrhea. All four GLP1RAs have the same warnings and contraindications for the risk of serious adverse effects, including medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2, and pancreatitis. There are currently no long-term cardiovascular outcome studies published with any GLP1RA.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the main benefit of albiglutide is its once weekly dosing regimen and lower incidence of nausea compared to the other GLP1RA drugs. The GLP1RAs will be re-reviewed at an upcoming meeting for UF and potential BCF placement.

Relative Cost-Effectiveness Analysis and Conclusion—Cost minimization (CMA) was performed to evaluate albiglutide (Tanzeum) with the other GLP1RA agents. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that albiglutide (Tanzeum) is cost-effective compared with other GLP1RA agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) albiglutide (Tanzeum) be designated formulary on the UF, based on clinical and cost effectiveness.

2. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** Existing automated PA (step therapy) criteria for the GLP1RAs requires a trial of metformin or a sulfonylurea first, based on positive long-term outcomes data with metformin and the sulfonylureas. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) PA criteria for albiglutide, requiring a trial of metformin or a sulfonylurea in all new and current users of albiglutide (Tanzeum), consistent with the PA requirements for the other GLP1RAs. Use of albiglutide is approved only for patients with Type 2 diabetes mellitus, consistent with the FDA-approved indication. (See Appendix C for full criteria.)

3. ***COMMITTEE ACTION***: ***PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) an effective date of the first Wednesday after a 30-day implementation period in all points of service (POS). Based on the P&T Committee's recommendation, the effective date is December 10, 2014.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Attention Deficit Hyperactivity Disorder (ADHD) Stimulants Subclass: Methylphenidate Extended Release (ER) Oral Suspension (Quillivant XR)

Background—Quillivant XR is FDA-indicated for the treatment of ADHD in children six years of age or older; it is dosed once daily. Quillivant XR delivers medication directly via a suspension, instead of opening capsules and mixing the beads or powder with food, which is required with other long-acting stimulants (e.g., Metadate CD, Ritalin LA, Adderall XR). There are no head-to-head studies comparing Quillivant XR to other ADHD medications. Current clinical practice guidelines suggest that all stimulant compounds indicated for ADHD

have very few differences among them in their ability to improve symptoms, their tolerability profiles, or risk of adverse events.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that although Quillivant XR offers the convenience of an oral suspension of methylphenidate ER, it failed to demonstrate clinically compelling advantages over existing UF agents for ADHD. Other long-acting stimulant preparations with alternative dosing formulations (e.g., sprinkles) are available on the UF.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to evaluate methylphenidate ER suspension (Quillivant XR) with other long-acting methylphenidate agents on the UF. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Quillivant XR was not cost-effective compared with other long-acting methylphenidate agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) methylphenidate ER oral solution (Quillivant XR) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) MN criteria for methylphenidate ER oral solution (Quillivant XR). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***
The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is February 18, 2014.

Director, DHA, Decision: ☒ Approved □ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Targeted Immunomodulatory Biologics (TIBs)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the TIBs Drug Class, which is comprised of the following injectable and oral medications:

- **Anti-tumor necrosis factor (TNF) biologics**: adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), and golimumab (Simponi)
- **Non-TNF biologics**: abatacept (Orencia), anakinra (Kineret), apremilast (Otezla), tocilizumab (Actemra), tofacitinib (Xeljanz), and ustekinumab (Stelara)

The TIBs are FDA-approved for a variety of indications, including rheumatologic, dermatologic, and gastrointestinal inflammatory conditions. The TIBs were reviewed for UF placement in November 2007 and adalimumab (Humira) was recommended as the only multi-indication TIB on the Extended Core Formulary (ECF). Since the 2007 class review, several new TIBs have been marketed. Two oral therapies, tofacitinib (Xeljanz) and apremilast (Otezla) are now available.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the TIBs, based on FDA-approved indications:

1. All the TIBs (adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, tofacitinib, anakinra, ustekinumab and apremilast) are highly effective for their FDA indications versus placebo, based on randomized controlled trials (RCTs).

2. There are few direct head-to-head trials between the TIBs; the majority of studies are non-inferiority trials. Comparative effectiveness is primarily determined though network meta-analysis (NMA) and indirect comparison; i.e., number needed to treat (NNT). The strength of evidence is typically low.

3. For rheumatoid arthritis, the available evidence is insufficient to clearly show superiority of one TIB over another with regard to the American College of Rheumatology 50 (ACR50) endpoint for response to treatment.

   In three systematic reviews, there was a trend favoring etanercept over the other TIBs in terms of efficacy. The same reviews found anakinra had a statistically significant lower mean response when compared to etanercept and adalimumab, but the strength of evidence was low.

4. For juvenile inflammatory arthritis, there is insufficient evidence to suggest clinically relevant differences between adalimumab and etanercept, the two TIBs approved in pediatric patients.

5. For psoriatic arthritis, due to the lack of head-to-head clinical trials and heterogeneous study populations, there is insufficient evidence to determine comparative efficacy between the four anti-TNFs (adalimumab, certolizumab, etanercept, and golimumab), and the non-TNFs (ustekinumab, and apremilast). Indirect comparisons from RCTs suggest similar NNTs for these drugs.

6. For psoriasis, three products are approved, adalimumab, etanercept, and ustekinumab. In one head-to-head RCT, ustekinumab was superior to etanercept

in achieving response, based on the Psoriasis Activity and Severity Index 75 (PASI 75) score. NMA demonstrated similar efficacy for adalimumab and ustekinumab.

7. For Crohn's disease, a NMA demonstrated that adalimumab and certolizumab are both effective for the induction of response and maintenance of remission and maintenance of response. The same analysis showed adalimumab is superior to certolizumab for induction of remission.

8. For ulcerative colitis, adalimumab and golimumab are effective for inducing clinical response, clinical remission, and mucosal healing. There is insufficient data for direct comparison of these agents.

9. With regard to safety, the overall rates of adverse events (AEs) are similar between the TIBs. In short-term trials, adalimumab and abatacept had a lower risk of serious AEs (serious infections, malignancies, lymphomas, withdrawals and other AEs) compared to other TIBs.

10. Evidence from indirect comparisons of two systematic reviews and one NMA shows the rate of serious infections is higher with certolizumab than the other TIBs. A subgroup analysis from one systematic review and a NMA showed the risk of serious infections was not increased with etanercept, in contrast to the increased risk seen with the other anti-TNF drugs, compared to controls.

11. The risk of tuberculosis (TB) is increased with the TIBs as a group. There is evidence (low strength) that suggests an increased risk with adalimumab, compared with etanercept.

12. The evidence (low strength) from indirect comparisons suggesting a safety benefit with etanercept in terms of serious infections and TB compared to the other anti-TNFs, must be weighed against its lack of efficacy for gastrointestinal conditions (Crohn's disease and ulcerative colitis).

13. Although the strength of evidence is low, there does not appear to be an elevated risk of malignancy with the TIBs. However, the risk of nonmelanoma skin cancer is increased with adalimumab and etanercept, compared to controls.

14. Concurrent use of a TIB with another TIB results in increased AEs and is not recommended by current practice guidelines.

15. Unique safety concerns with the non-TNF biologics include the following:

    - abatacept: Increased risk of chronic obstructive pulmonary disease (COPD) exacerbation in adults with COPD
    - tocilizumab and tofacitinib: gastrointestinal perforation and lab abnormalities, including elevated lipids and transaminases

- apremilast: psychiatric adverse effects such as depression and suicidal ideations

16. Overall, adalimumab has the highest clinical utility within the Military Health System (MHS) given its seven FDA-approved indications and wide spectrum of clinical coverage.
17. Inclusion of a non-TNF biologic on the formulary is required for patients who do not respond to an anti-TNF biologic.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and budget impact analysis (BIA) were performed to evaluate the TIBs used to treat rheumatologic (stratified by rheumatoid arthritis and psoriatic arthritis), dermatologic, and gastrointestinal (stratified by Crohn's disease and ulcerative colitis) inflammatory conditions. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

1. CMA results for the TIBs showed the following:
    - For rheumatoid arthritis, adalimumab (Humira) was the most cost-effective TIB, followed by certolizumab (Cimzia), anakinra (Kineret), tofacitinib (Xeljanz), golimumab (Simponi), etanercept (Enbrel), abatacept (Orencia), and tocilizumab (Actemra).
    - For psoriatic arthritis, adalimumab was the most cost-effective drug, followed by apremilast (Otezla), certolizumab, golimumab, etanercept, and ustekinumab (Stelara).
    - For dermatologic conditions, adalimumab was the most cost-effective TIB, followed by etanercept, and ustekinumab.
    - For gastrointestinal conditions (Crohn's disease), adalimumab was the most cost-effective agent, followed by certolizumab. For ulcerative colitis, adalimumab was the most cost-effective agent, followed by golimumab.
2. A BIA was performed to evaluate the potential impact of scenarios, with selected agents designated step-preferred and UF or non-preferred and NF.

Robust BIA results showed the scenario with adalimumab designated as formulary and step preferred on the UF; apremilast, golimumab, tofacitinib, and ustekinumab designated as formulary and non-preferred; and, abatacept, anakinra, certolizumab, etanercept, and tocilizumab designated as NF and non-step preferred, was the most cost-effective option for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 0 absent) the following for the TIBs, based on clinical effectiveness, and cost effectiveness.

- UF and step-preferred ("in front of the step"): adalimumab (Humira)
- UF and non-preferred ("behind the step"): apremilast (Otezla), golimumab (Simponi), tofacitinib (Xeljanz), and ustekinumab (Stelara)
- NF and non-preferred: abatacept (Orencia), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), and tocilizumab (Actemra)
- This recommendation includes step therapy, which requires a trial of adalimumab for all new users of a TIB.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent), adalimumab (Humira) be designated BCF upon signing of the minutes. The TIBs are now classified as a BCF rather than an ECF drug class. Military Treatment Facilities (MTFs) that do not currently have adalimumab on formulary are required to add it to their local formularies and make it available to beneficiaries on the same basis as any other BCF agent.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) MN criteria for abatacept (Orencia), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), and tocilizumab (Actemra). (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—Existing manual PA criteria currently apply to all the TIBs. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) automated (step therapy) criteria for all new users of the non-preferred TIBs [abatacept (Orencia), anakinra (Kineret), apremilast (Otezla), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), tocilizumab (Actemra), tofacitinib (Xeljanz), and ustekinumab (Stelara)], requiring a trial of adalimumab (Humira) before the non-step preferred drugs.

   A trial of Humira is not required if:

   - Contraindications exist to Humira
   - The patient has had an inadequate response to Humira, and requires a different anti-TNF biologic or a non-TNF biologic
   - The patient has experienced adverse reactions to Humira which are not expected to occur with the requested non-preferred TIB
   - There is no formulary alternative for the following:
     - Enbrel: Patient is a child younger than four years of age or the patient has hepatitis C virus

- Non-TNF TIB (Orencia, Actemra, Xeljanz, Kineret, Stelara, and Otezla): Patient has symptomatic chronic heart failure
- Actemra, Orencia or Simponi: Patient has been stable on an intravenous formulation, with continuous use in the past three months and needs to transition to the subcutaneous formulation

The P&T Committee also recommended manual PA criteria for all users of Humira or a non-preferred TIB. Coverage for the TIBs is only allowed for the FDA-approved indications, and coverage is not approved for concomitant use of a TIB with other biologics. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—QLs currently apply to the TIBs. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) to continue the current QLs for abatacept, adalimumab, anakinra, apremilast, certolizumab, etanercept, golimumab, tofacitinib, tocilizumab, and ustekinumab, at a maximum of a 28-day supply in the Retail Network and maximum of a 56-day supply in the Mail Order Pharmacy.

6. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is February 18, 2014.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. BCF CHANGES

A. Non-Insulin Diabetes Drugs—Sulfonylureas: MTF Request for Glyburide Deletion from the BCF

The P&T Committee reviewed a MTF request to delete glyburide from the BCF. Two sulfonylureas, glyburide (Diabeta, Glynase, generics) and glipizide (Glucotrol, generics) have been maintained on the BCF since 1998. Two other sulfonylureas, glimepiride (Amaryl, generics) and glipizide XL (Glucotrol XL, generics) are designated UF. Glipizide is safer to use than glyburide in diabetic patients with renal insufficiency.

However, glyburide is the sulfonylurea of choice for treating pregnant women, based on an article in the New England Journal of Medicine from 2000. P&T Committee members were concerned about the availability of glyburide for pregnant patients at all MTFs if it was removed from the BCF.

1. ***COMMITTEE ACTION: GLYBURIDE DELETION FROM THE BCF***
   The P&T Committee recommended (0 for, 17 opposed, 0 abstained, 0 absent) to remove glyburide on the BCF. Glyburide will be retained on the BCF. Providers are cautioned about the risk of renal insufficiency with glyburide.

B. Contraceptives Agents (Triphasics): Ethinyl Estradiol (EE) 25 mcg; Norgestimate 0.18/0.215/0.25mg (Ortho Tri-Cyclen Lo, generics) Deletion from the BCF

The P&T Committee reviewed trends in utilization and spend for the Contraceptives Agents. Multiple generic entrants, product discontinuations, and pricing changes frequently occur for the various products. Eleven contraceptive subclasses are on the BCF, including six monophasic, one triphasic, and one progestogen-only formulation; all the contraceptive subclasses have designated UF products.

The triphasic product EE 25 mcg with 0.18/0.215/0.25mg norgestimate (Ortho Tri-Cyclen Lo) has been maintained on the BCF since May 2006. An increase in the Ortho Tri-Cyclen Lo price has been noted over the past two years. Other triphasic products with EE 25 mcg, containing a different progestin (e.g., desogestrel in the formulations of Cyclessa and Velivet) and norgestimate-containing products with EE 35 mcg (e.g., Ortho Tri-Cyclen and Trinessa) are available on the UF at significant cost savings.

1. ***COMMITTEE ACTION: EE 25 MCG; 0.18/0.215/0.25MG NORGESTIMATE (ORTHO TRI-CYCLEN LO) DELETION FROM THE BCF***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) removing EE 25 mcg; 0.18/0.215/0.25mg norgestimate (Ortho Tri-Cyclen Lo) from the BCF upon signing of the minutes; the drug remains UF.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VII. UTILIZATION MANAGEMENT

A. PA and QLs

1. **Valeritas V-Go Insulin Delivery Device**—V-Go is a disposable insulin delivery device approved for patients with Type 2 diabetes mellitus. Unlike an insulin pump, V-Go does not require any tubing or catheters. The device is filled daily with rapid acting insulin, allowing for continuous administration of basal insulin. After 24 hours, the

device is discarded and replaced with a new unit. Advantages of V-Go include convenience to the patient desiring increased control over their blood glucose levels and elimination of the need for multiple daily insulin injections. Additionally, V-Go may reduce prandial glycemic excursions compared to multiple insulin injections. Potential disadvantages of V-Go include the risk of hypoglycemia and infection, the requirement for daily manual filling of the device with insulin, non-adjustable preset basal rates, and the potential for wastage.

The P&T Committee considered PA criteria for V-Go, consistent with the product labeling, including the capacity and purpose of the system (a maximum allowable dose of insulin of 76 units per day), and the meal time bolus insulin dose capability (no less than 2 unit increments of insulin).

a) ***COMMITTEE ACTION: V-GO MANUAL PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) manual prior authorization criteria for all new users of V-Go. Coverage will be approved if the patient meets all of the following criteria:

(1) Patient has Type 2 diabetes mellitus; AND

(2) Patient does not need more than 40 units of basal insulin daily AND the patient does not need more than 36 units of bolus insulin daily; AND

(3) Patient does not need less than 2 unit increments of bolus dosing; AND

(4) Patient has been maintained on stable basal insulin for at least three months (at dosages of 20U, 30U, or 40U); AND

(5) Patient has been using prandial insulin for at least three months.

b) ***COMMITTEE ACTION: V-GO QLS***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) QLs of 30 units per 30 days, consistent with the product labeling of 1 unit used daily.

c) ***V-GO PA IMPLEMENTATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) implementation of the PA upon signing of the minutes.

2. **Newer Sedative Hypnotics (SED-1s): Tasimelteon (Hetlioz)**—Tasimelteon is a melatonin receptor agonist that is approved for treating blind patients who have non-24 hours sleep-wake disorder and have no light perception. It will be reviewed as a new drug at an upcoming meeting. Automated PA (step therapy) currently applies to the SED-1s Drug Class, where a trial of generic zolpidem immediate release (IR) or zaleplon is required first.

a) ***COMMITTEE ACTION: TASIMELTEON (HETLIOZ) PA CRITERIA***
The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) PA criteria for all new users of tasimelteon (Hetlioz) who are blind and have non-24 hour sleep-wake disorder. PA criteria will require a trial of generic zolpidem IR or zaleplon before Hetlioz. (See Appendix C for full criteria.)

b) ***COMMITTEE ACTION: TASIMELTEON (HETLIOZ) PA IMPLEMENTATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) an effective date of no later than the first Wednesday after a 30-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is December 10, 2014.

3. **Metastatic Melanoma Medications: Trametinib (Mekinist) and Dabrafenib (Tafinlar) Manual PA Criteria**—Mekinist and Tafinlar are oral kinase inhibitors approved for treating patients with unresectable or metastatic melanoma who have documented BRAF V600E or V600K mutations as detected by an FDA-approved test. PA criteria currently apply to other oral kinase inhibitors for this diagnosis.

   a) ***COMMITTEE ACTION: TRAMETINIB (MEKINIST) AND DABRAFENIB (TAFINLAR) PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria should apply to all new users of Mekinist and Tafinlar, consistent with the FDA-approved product labeling. The PA will ensure that candidates likely to respond to Mekinist and Tafinlar are identified prior to initiating therapy. (See Appendix C for full criteria.)

4. **Seizure Medications: Topiramate ER capsules (Trokendi XR and Qudexy XR) Manual PA Criteria**—Trokendi XR and Qudexy XR are branded ER formulations of topiramate that are dosed once daily. Generic formulations of topiramate IR have been marketed since 1996, and include both tablets and capsules. Generic topiramate IR is FDA-approved for treating patients with seizures, down to the age of two years, and migraine headache. Topiramate is sometimes used off –label for weight loss.

   Trokendi XR and Qudexy XR are indicated for the treatment of seizures, but are only approved for patients down to the age of six or ten years, depending on the diagnosis.

   a) ***COMMITTEE ACTION: TOPIRAMATE ER (TROKENDI XR AND QUDEXY XR) PA CRITERIA***—The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 0 absent) PA criteria for all new users of Trokendi XR and Qudexy XR consistent with the product's labeling for treatment of seizures, due to the potential for off-label use. Patients will be required to try generic topiramate IR first, unless there is a contraindication or adverse reaction with the generic product. (See Appendix C for full criteria.)

b) ***COMMITTEE ACTION: TOPIRAMATE ER (TROKENDI XR AND QUDEXY XR) PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) an effective date no later than the first Wednesday after a 30-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is December 10, 2014.

5. **Oral Chemotherapy Agents: Ibrutinib (Imbruvica), Idealisib (Zydelig), and Everolimus (Afinitor Disperz)**—QLs currently apply to the oral chemotherapy agents.

a) ***COMMITTEE ACTION: IBRUTINIB (IMBRUVICA), IDEALISIB (ZYDELIG,) AND EVEROLIMUS (AFINITOR DISPERZ)—QLs***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following QLs, consistent with the products' packaging and labeling:

(1) Ibrutinib (Imbruvica): A maximum allowable quantity at the retail network POS of 60 tablets (30-day supply) and 120 tablets at the Mail Order Pharmacy (60-day supply)

(2) Idealisib (Zydelig): A maximum allowable quantity at the retail network POS of 60 tablets (30-day supply) and 120 tablets at the Mail Order Pharmacy (60-day supply)

(3) Everolimus (Afinitor Disperz): A maximum allowable quantity at the retail network POS of a 28-day supply, and a 56-day supply at the Mail Order Pharmacy.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. SECTION 716 OF THE NATIONAL DEFENSE AUTHORIZATION ACT (NDAA) FISCAL YEAR 2013 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM

A. Medication Drug List for the Pilot Program: Updates—The Medication Drug list for the Pilot Program for TRICARE for Life beneficiaries was recommended at the November 2013 P&T Committee meeting. An update to the drug list is required due to some products being discontinued from the market, availability issues, and to ensure consistency within the drug classes. (See the November 2013 P&T Committee meeting minutes, Appendix F, found at

http://pec.ha.osd.mil/PT_min_charter.php?submenuheader=5
or the TRICARE Formulary Search Tool at
http://pec.ha.osd.mil/TFL_maintenance_drug_list.php for the full medication drug list.)

1. ***COMMITTEE ACTION: MAINTENANCE MEDICATION PROGRAM DRUG LIST UPDATE***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following changes to the list of covered maintenance medications for the Section 716 pilot program. Implementation will occur upon signing of the minutes.

    - Remove from list due to manufacturer discontinuation: Cardizem 90 mg tablet; Dilacor XR 240 mg capsule; Estraderm 0.05 mg patch; Exelon 2 mg/mL solution; Lantus 100 units/mL cartridge; Lufyllin-GG elixir; Namenda 5mg–10 mg titration pack; Parcopa 10 mg–100 mg orally dissolving tablet (ODT); Parcopa 25 mg–100 mg ODT; Parcopa 25 mg–250 mg ODT; Potaba 500 mg tablet; Questran Light packet; Sanctura XR 60 mg capsules; Teveten 400 mg tablets; Uniretic 15mg–25 mg tablet
    - Remove from list due to noncompliance with the Trade Agreements Act: Isopoto carpine 2% eye drops; Lopid 600 mg tablet; Pepcid 40 mg tablet
    - Remove from list due to availability issues: Theo24
    - Add to list, due to consistency with the drug class: Humulin 70/30 Kwikpen; Humilin 100 units/mL Kwikpen; Pegasys 180 mcg/0.5 mL syringe
    - Add to list due to consistency with the class and UF changes recommended at the August 2014 P&T Committee meeting: TIBs formulary drugs—Otezla, Simponi, Stelara, and Xeljanz

    Director, DHA, Decision: ☒ Approved ☐ Disapproved

    Approved, but modified as follows:

IX. LINE EXTENSIONS

A. Formulary Status Clarification—The P&T Committee clarified the formulary status for one product line extension ("follow-on product") by the original manufacturer. Line extensions have the same FDA indications and pricing as the "parent" drug. The product is a new dosage strength of buprenorphine transdermal system (Butrans).

1. ***COMMITTEE ACTION: LINE EXTENSIONS FORMULARY STATUS CLARIFICATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) clarifying the formulary status of the following product to reflect

the current formulary status and step therapy/PA criteria of the parent compound. Implementation will occur upon signing of the minutes.

- Buprenorphine patch (Butrans) 7.5 mcg/hour patch: UF with PA, similar to Butrans patch 5, 10, 15, and 20 mcg/hour

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

X. FISCAL YEAR 2008 NDAA, Section 703

The P&T Committee reviewed drugs from manufacturers that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not in compliance with the Fiscal Year 2008 NDAA, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the Retail POS and medical necessity in the MTFs. These NF drugs will remain available in the Mail Order POS without preauthorization.

1. ***COMMITTEE ACTION: DRUGS DESIGNATED NF***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) that the following products be designated NF on the UF:

Auxilium Pharma:	Robaxin 750, Robaxin, Levatol
Bluepoint Lab:	Nitrofurantoin Mono-M; Nitrofurantoin
Eli Lilly:	Livalo
Kowa:	Livalo
Major Pharma:	sulfasalazine, methotrexate
Orexo:	Zubsolv
Purdue:	Dilaudid, Intermezzo
VistaPharm:	sucralfate
Xenoport:	Horizant
Zylera:	Ulesfia

2. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following pre-authorization criteria for the drugs recommended NF above: 1) obtaining the product by home delivery would be detrimental to the patient; and, 2) for branded products with AB generic availability, use of the generic product would be detrimental to the patient. These pre-authorization criteria do not apply to any POS other than retail network pharmacies.

3. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD FOR PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in the Retail Network; and, 2) DHA send a letter to beneficiaries affected by these decisions. Based on the P&T Committee's recommendation, the effective date is February 18, 2014.

4. ***COMMITTEE ACTION: DRUG DESIGNATED FORMULARY***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) retaining the following drugs, due to their unique clinical niches: oxycodone 5 mg/mL solution (VistaPharm); nitrogen mustard topical gel for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (Valchlor; Actelion); and, typhoid vaccine live oral (Vivotif; Berne Products Crucell).

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

XI. ITEMS FOR INFORMATION

A. Specialty Medications—The P&T Committee was briefed on an initial plan for specialty medications, including a discussion of a proposed definition of a specialty agent. DHA's goal is to provide a standardized means to measure utilization and spend of specialty agents, and to evaluate patient outcomes. Other aspects include providing tools to assist patients, providers, and MTFs in the course of managing drug and associated therapy for these complex disease states. The P&T Committee will receive updates and will review specialty agents eligible for contractor-provided clinical pharmacy services at future meetings.

XII. ADJOURNMENT

The meeting adjourned at 1730 hours on August 13, 2014. The next meeting will be in November 2014.

Appendix A—Attendance: August 2014 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix E—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

13 Nov 2014
Date

Appendix A—Attendance: August 2014 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
Dr. George Jones	Chief, DHA Pharmacy Operations Division
LTC Robert Conrad, MS	Chief, DHA Pharmacoeconomic Branch (Recorder)
COL John Spain, MS	Army, Pharmacy Officer
Col Scott Sprenger, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Derrik Clay for CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
COL Ted Cieslak, MC	Army, Physician at Large
Col Michael Wynn, MC	Army, Family Practice Physician
LCDR Carey Welsh, MC	Navy, Pediatrics Physician
Col James Jablonski, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Larissa Weir, MC	Air Force, OB/GYN Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Voting Members Absent	
Col Michael Spilker, BSC	DHA Deputy Chief, Pharmacy Operations Division
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, DHA
CDR Brandon Hardin by phone	Medical Logistics Division, DLA
Guests	
Lt Col Dan Castiglia	Defense Logistics Agency Troop Support
Capt Richard Caballero	Defense Logistics Agency Troop Support

Appendix A—Attendance (continued)

Guests—(continued)	
LCDR Robert Selvester, MC	VA/DoD Evidence-Based Practice Guideline Work Group
Mr. Alexander Quinones	Defense Logistics Agency Troop Support
CDR Matthew Baker	Indian Health Service
CDR Brandon Hardin via DCO	Medical Logistics Division, DLA
Ms. Nancy Misel via DCO	Air Force, Pharmacy Officer
CAPT Brittany Latimer via DCO	Army, Pharmacy Officer
MAJ Kevin Ridderhoff via DCO	DHA, Pharmacy Operations Division
LT Kendra Jenkins via DCO	DHA, Pharmacy Operations Division
Others Present	
CAPT Walter Downs, MC	DHA Pharmacoeconomic Branch
CDR Joshua Devine, USPHS	DHA Pharmacoeconomic Branch
CDR Edward Vonberg, BSC	DHA Pharmacoeconomic Branch
LCDR Marisol Martinez, USPHS	DHA Pharmacoeconomic Branch
Maj David Folmar, BSC	DHA Pharmacoeconomic Branch
MAJ Misty Cowan, MC	DHA Pharmacoeconomic Branch
Maj Ronald Khoury, MC	DHA Pharmacoeconomic Branch
Dr. David Meade	DHA Pharmacoeconomic Branch
Dr. Angela Allerman	DHA Pharmacoeconomic Branch
Dr. Eugene Moore	DHA Pharmacoeconomic Branch
Dr. Shana Trice	DHA Pharmacoeconomic Branch
Dr. Teresa Anekwe via DCO	DHA Pharmacoeconomic Branch
Dr. Amy Lugo via DCO	DHA Pharmacoeconomic Branch
Dr. Brian Beck	DHA Pharmacoeconomic Branch
Mr. Kirk Stocker	DHA Pharmacoeconomic Branch contractor
Ms. Deborah Garcia	DHA Pharmacoeconomic Branch contractor
Dr. Esmond Nwokeji	DHA Pharmacoeconomic Branch contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Abatacept (Orencia) • Anakinra (Kineret) • Certolizumab (Cimzia) • Etanercept (Enbrel) • Tocilizumab (Actemra) **Targeted Immunomodulatory Biologics (TIBs)**	• Use of adalimumab (Humira) is contraindicated • The patient has experienced or is likely to experience significant adverse effects from adalimumab (Humira) • Adalimumab (Humira) resulted or is likely to result in therapeutic failure. • The patient previously responded to the nonformulary agent and changing to adalimumab (Humira) would incur unacceptable risk • No alternative formulary agent applies only to: 1. Abatacept (Orencia): The patient is transitioning from IV abatacept or has symptomatic congestive heart failure CHF. 2. Anakinra (Kineret): The patient has neonatal onset multisystem inflammatory disease (NOMID), a subtype of cryopyrin associated periodic syndrome (CAPS). 3. Etanercept (Enbrel): The patient is less than 4 years of age or has hepatitis C infection. 4. Tocilizumab (Actemra): The patient is transitioning from IV abatacept or has symptomatic CHF. **Formulary alternative:** adalimumab (Humira)
• Methylphenidate ER oral suspension (Quillivant XR) **Attention Deficit Hyperactivity Disorder Stimulants**	• The formulary agents resulted in therapeutic failure. • No alternative formulary agent — patient has a G-tube. **Formulary alternatives:** Methylphenidate immediate release, sustained release, or extended release

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Adalimumab (Humira) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis, active psoriatic arthritis, or active ankylosing spondylitis • Moderate to severe chronic plaque psoriasis who are candidates for systemic or phototherapy, and when other systemic therapies are medically less appropriate • Moderate to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to Remicade, or an inability to tolerate Remicade • Moderate to severely active ulcerative colitis following inadequate response to immunosuppressants Coverage approved for pediatric patients (age 4-17 years) with: • Moderate to severe active polyarticular juvenile idiopathic arthritis Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Golimumab (Simponi) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not me, coverage is approved for Simponi if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira is not expected with requested non-step preferred TIB • Patient has been stable on IV Simponi with continuous use in last 3 months and needs to transition to the SC formulation of Simponi AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis in combination with methotrexate • Active psoriatic arthritis or active ankylosing spondylitis • Moderately to severely active ulcerative colitis with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy Rheumatoid arthritis patients require an active methotrexate script. Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)

Drug / Drug Class	Prior Authorization Criteria
• Certolizumab (Cimzia) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Cimzia if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis, active psoriatic arthritis, or active ankylosing spondylitis • Moderately to severely active Crohn's disease following an inadequate response to conventional therapy. Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Etanercept (Enbrel) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Enbrel if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative (Enbrel is prescribed for children < 4years of age; Enbrel is prescribed for a patient with hepatitis C virus) AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis, active psoriatic arthritis, or active ankylosing spondylitis • Moderate to severe chronic plaque psoriasis who are candidates for systemic or phototherapy Coverage approved for pediatric patients (age 2–17) with: • Moderate to severe active polyarticular Juvenile Idiopathic Arthritis Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)

Drug / Drug Class	Prior Authorization Criteria
• Anakinra (Kineret) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria If automated criteria are not met, coverage is approved for Kineret if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative (Kineret for pediatric patient with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a subset of Cryoprin Associated Period Syndrome (CAPS) NOMID • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis, who have failed ≥ 1 disease modifying anti-rheumatic drugs (DMARDs) Coverage approved for pediatric patients (all ages) with: • Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a subset of Cryoprin Associated Period Syndrome (CAPS) Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Abatacept (Orencia) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Orencia if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF • Patient has been stable on IV Orencia with continuous use in last 3 months and needs to transition to the SC formulation of Orencia AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis • Subcutaneous Orencia is not approved for use in systemic or polyarticular Juvenile Idiopathic Arthritis

Drug / Drug Class	Prior Authorization Criteria
	Abatacept (Orencia)—continued Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Tocilizumab (Actemra) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Actemra if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF • Patient has been stable on an IV TIB with continuous use in last 3 months and needs to transition to the SC formulation of Actemra AND Coverage approved for patients ≥ 18 years with: • Moderate to severe active rheumatoid arthritis who have had an inadequate response to ≥ 1 disease modifying anti-rheumatic drugs (DMARDs) • Subcutaneous Actemra is not approved for use in systemic or polyarticular Juvenile Idiopathic Arthritis Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Tofacitinib (Xeljanz) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Xeljanz if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • Adverse reactions to Humira not expected with requested non-step preferred TIB • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF AND Coverage approved for patients ≥ 18 years with: • Moderate to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

Drug / Drug Class	Prior Authorization Criteria
	Tofacitinib (Xeljanz)—continued Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Apremilast (Otezla) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Otezla if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF • Adverse reactions to Humira not expected with requested non-step preferred TIB AND Coverage approved for patients ≥ 18 years with: • Active psoriatic arthritis Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• Ustekinumab (Stelara) **Targeted Immunomodulatory Biologics (TIBs)**	Automated PA criteria: The patient has filled a prescription for adalimumab (Humira) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria: If automated criteria are not met, coverage is approved for Stelara if: • Contraindications exist to Humira • Inadequate response to Humira (need for different anti-TNF or non-TNF) • There is no formulary alternative: patient requires a non-TNF TIB for symptomatic CHF • Adverse reactions to Humira not expected with requested non-step preferred TIB AND Coverage approved for patients ≥ 18 years with: • Active psoriatic arthritis • Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Drug / Drug Class	Prior Authorization Criteria
	Ustekinumab (Stelara)—continued Coverage is NOT provided for concomitant use other TIBs including but not limited to adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz), ustekinumab (Stelara), apremilast (Otezla), or rituximab (Rituxan)
• albiglutide once weekly (Tanzeum) **Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)**	All new and current users of albiglutide (Tanzeum) are required to try metformin or a sulfonylurea (SU) before receiving Tanzeum. Automated PA criteria: The patient has received a prescription for metformin or SU at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days, AND Manual PA criteria: If automated criteria are not met, albiglutide (Tanzeum) is approved (e.g., trial of metformin or SU is NOT required) if: • The patient has a confirmed diagnosis of Type 2 Diabetes Mellitus • The patient has experienced any of the following issues on metformin: o impaired renal function precluding treatment with metformin o history of lactic acidosis • The patient has experienced any of the following issues on a sulfonylurea: o hypoglycemia requiring medical treatment • The patient has had inadequate response to metformin or a SU • The patient has a contraindication to metformin or a SU
• Valeritas V-Go Insulin Delivery Device (V-Go) **Insulins**	PA criteria apply to all new users of the V-Go device. Manual PA criteria: (1) Patient has Type 2 diabetes mellitus AND (2) Patient does not need more than 40 units of basal insulin daily AND the patient does not need more than 36 units of bolus insulin daily AND (3) Patient does not need less than 2 unit increments of bolus dosing AND (4) Patient has been maintained on stable basal insulin for at least 3 months (at dosages of 20U, 30U, or 40U) AND (5) Patient has been using prandial insulin for at least 3 months.
• Tasimelteon (Hetlioz) **Newer Sedative Hypnotic-1s**	PA criteria apply to all new users of tasimelteon (Hetlioz). A trial of generic zolpidem IR or zaleplon is required before Hetlioz. Automated PA: The patient has filled a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA: If automated criteria are not met, tasimelteon (Hetlioz) is approved (e.g., trial of zolpidem immediate release or zaleplon is NOT required) if the patient meets criterion #1 below, and one of the other criteria (#2, #3, or #4).

Drug / Drug Class	Prior Authorization Criteria
	Tasimelteon (Hetlioz)—continued (1) The patient is totally blind and has no light perception. AND (2) The patient has received a trial of zolpidem IR or zaleplon and had an inadequate response. OR (3) The patient received a trial of zolpidem IR or zaleplon but was unable to tolerate it due to adverse effects. OR (4) Treatment with zolpidem IR or zaleplon is contraindicated for this patient (e.g., due to hypersensitivity, aberrant behaviors, or intolerable rebound insomnia).
• Trametinib (Mekinist) and Dabrafenib (Tafinlar) **Metastatic Melanoma Medications**	Manual PA criteria apply to all new users of trametinib (Mekinist) and dabrafenib (Tafinlar) Mekinist: • Coverage approved for treatment of patients alone or in combination with dabrafenib (Tafinlar) in patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. • Coverage not approved as a single agent in patients who have received prior BRAF-inhibitor therapy Tafinlar: • Coverage approved as a single agent for treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. • Combination use with Mekinist in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. • Not approved for patients with wild-type BRAF melanoma
• Topiramate ER (Trokendi XR and Qudexy XR) **Seizure Medications**	Manual PA criteria apply to all new users of Trokendi XR and Qudexy XR: • Coverage approved for o Partial onset seizure and 1° generalized tonic-clonic seizures in patients ≥ 10 years o Lennox-Gastaut seizures in patients ≥ 6 years • Coverage not approved for o Non-FDA approved indications, including migraine headache and weight loss • Patient is required to try topiramate first, unless the following has occurred: o Inadequate response not expected to occur with Trokendi XR or Qudexy XR o Patient has contraindication or adverse reaction to a component of generic topiramate not expected to occur with Trokendi XR or Qudexy XR

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2014	**Targeted Immunologic Biologics**	UF class review Previously reviewed	▪ Adalimumab (Humira)	▪ Apremilast (Otezla) ▪ Golimumab (Simponi) ▪ Tofacitinib (Xeljanz) ▪ Ustekinumab (Stelara)	▪ Abatacept (Orencia ▪ Anakinra (Kineret) ▪ Certolizumab (Cimzia) ▪ Etanercept (Enbrel) ▪ Tocilizumab (Actemra)	Pending singing of the minutes / 90 days	▪Step therapy required; see comments ▪Quantity Limits apply; see Formulary Search Tool	▪ Must try Humira first in all new users before the other TIBs. (See Appendix C) ▪ TIBs are no longer an ECF class; Humira now BCF

TRICARE Formulary Search tool: *http://www.pec.ha.osd.mil/formulary_search.php*

Appendix E—Table of Abbreviations

A1c	hemoglobin A1c
ACR50	American College of Rheumatology 50
ADHD	attention deficit hyperactivity disorder
AE	adverse event
BCF	Basic Core Formulary
BIA	budget impact analysis
CAPS	Cryoprin Associated Period Syndrome
CEA	cost-effectiveness analysis
CHF	congestive heart failure
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DCO	Defense Connect Online
DHA	Defense Health Agency
DMARDs	disease modifying anti-rheumatic drugs
DoD	Department of Defense
DR	delayed release
EE	ethinyl estradiol
ER	extended release
ECF	Extended Core Formulary
FDA	U.S. Food and Drug Administration
GLP1RA	glucagon-like peptide-1 receptor agonist
IR	immediate release
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
NDAA	National Defense Authorization Act
NOMID	Neonatal-Onset Multisystem Inflammatory Disease
NMA	network meta-analysis
NNT	number needed to treat
P&T	Pharmacy and Therapeutics
PA	prior authorization
PASI 75	Psoriasis Activity and Severity Index 75
POS	points of service
RCTs	randomized controlled trials
QLs	quantity limits
SED-1s	Newer Sedative Hypnotics Drug Class
SU	sulfonylurea
TB	tuberculosis
TIBs	targeted immunomodulatory biologics
TNF	tumor necrosis factor
UF	Uniform Formulary

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

February 2014

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 12, 2014, at the Defense Health Agency (DHA) Pharmacoeconomic Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Lt. Gen. Douglas J. Robb, DO, MPH, Director, DHA, approved the minutes for the November 2013 DoD P&T Committee meeting on February 10, 2014.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Antidepressants (AD-1s)—Bupropion extended release 450 mg (Forfivo XL), desvenlafaxine extended release (ER) (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix).

Background and Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 against, 0 absent, 0 abstain) the following with regard to the clinical efficacy and safety of bupropion XL 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix). All four drugs are indicated solely for the treatment of major depressive disorder (MDD).

1. Forfivo XL

    a) Forfivo XL is an extended-release 450 mg formulation of bupropion, a norepinephrine/dopamine reuptake inhibitor (NDRI). Several generic formulations of bupropion (Wellbutrin, Wellbutrin SR, and Wellbutrin XL) are on the BCF. There are no clinical trials with Forfivo XL; FDA approval was based on demonstrated bioequivalence to three tablets of 150 mg Wellbutrin XL.

    b) Limitations to the product include that patients must be titrated with another bupropion formulation first, and the dose cannot be adjusted in renal or hepatic impairment.

    c) Forfivo XL has similar safety and tolerability concerns as other bupropion agents.

    d) While Forfivo XL offers an alternative treatment option of one tablet administered once daily for patients requiring a high dose of bupropion, it offers no compelling clinical advantages over the other bupropion formulations on the BCF or UF.

2. Desvenlafaxine ER (Khedezla)

    a) Khedezla is a serotonin/norepinephrine reuptake inhibitor (SNRI) that is an extended-release form of desvenlafaxine (Pristiq). Khedezla differs from Pristiq in the salt form (desvenlafaxine base versus desvenlafaxine succinate). Generic desvenlafaxine formulations are now available.

    b) Khedezla has shown bioequivalence to Pristiq in three studies; there are no clinical trials available.

    c) Khedezla offers no clinically relevant advantages over the venlafaxine products (Effexor, Effexor XR, generic) products on the UF.

3. Levomilnacipran (Fetzima)

    a) Levomilnacipran is a SNRI and is an extended-release stereoisomer of milnacipran (Savella). Fetzima is indicated for MDD whereas Savella is indicated for fibromyalgia.

    b) There are no head-to-head studies comparing levomilnacipran with other antidepressants.

    c) In the three placebo-controlled studies used to gain FDA approval, all levomilnacipran doses produced a statistically significant change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS). However, varying effects on response rates (e.g., a 50% reduction in the MADRS score from baseline) have been reported, depending on the dose and study design. There was no difference from placebo in remission rate at any levomilnacipran dose.

d) The safety profile of levomilnacipran is similar to milnacipran (Savella) and carries the same warnings.

e) Levomilnacipran offers no clinically compelling advantages over the other AD-1s on the UF.

4. Vortioxetine (Brintellix)

a) There have been no head-to-head studies between vortioxetine and other antidepressants. In four of seven placebo-controlled studies, vortioxetine was superior to placebo in improving MADRS or HAMD (Hamilton Depression Rating Scale) scores from baseline.

b) In active comparator studies using duloxetine (Cymbalta) or venlafaxine (Effexor), vortioxetine showed similar clinical results in the endpoints of MADRS, HAMD, response, or remission.

c) The most common adverse events (AEs) with vortioxetine include nausea and vomiting. Vortioxetine has fewer known AEs and warnings compared to desvenlafaxine, duloxetine (Cymbalta), and levomilnacipran. However, vortioxetine is the newest AD-1 to reach the market and additional AEs may increase during post-marketing surveillance.

d) Although vortioxetine offers additional serotonergic effects in its mechanism of action and has fewer AEs overall than some of the other AD-1s, this has not translated into greater efficacy in treating depression.

Relative Cost-Effectiveness Analysis and Conclusion—Cost minimization analysis (CMA) was performed to evaluate new antidepressants bupropion XL 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix) compared with other AD-1 subclasses, including selective serotonin reuptake inhibitors (SSRIs), SNRIs, and NDRIs. Based on the CMA results, the P&T Committee concluded (16 for, 0 against, 0 absent, 0 abstain) the following:

- For the NDRIs, the current BCF drugs—generic bupropion IR, sustained release and ER formulations—were the most cost-effective agents, followed by the new entrant Forfivo XL and then followed by the NF branded product bupropion hydrobromide (Aplenzin).

- For the SNRIs and SSRIs subclasses, the BCF drugs citalopram and sertaline were the most cost-effective drugs, followed by generic venlafaxine IR and ER, and then followed by generic desvenlafaxine, Khedezla, generic duloxetine (Cymbalta), levomilnacipran (Fetzima), vortioxetine (Brintellix), and branded duloxetine (Cymbalta), ranked in order from most to least cost effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) bupropion XL 450 mg

(Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix) be designated NF, based on clinical and cost effectiveness. Additionally, the P&T Committee recommended Khedezla, Fetzima, and Brintellix be non-step preferred ("behind the step"), which requires a trial of a formulary AD-1 prior to use in all current and new patients. See Prior Authorization section, below.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) MN criteria for bupropion 450 mg XL (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) PA criteria should apply to Khedezla, Fetzima, and Brintellix. (See Appendix C for the full PA criteria.)

    a) Desvenlafaxine ER (Khedezla): For all new users of Khedezla, patients are required to try venlafaxine immediate release (IR) or ER (Effexor, Effexor XR; generics) first.

    b) Levomilnacipran (Fetzima) and vortioxetine (Brintellix): For new users of Fetzima or Brintellix, patients are required to try a generic SSRI, duloxetine, SNRI (except milnacipran), tricyclic antidepressant, mirtazapine, bupropion, serotonin antagonist reuptake inhibitor (trazodone or nefazodone), or mononamine oxidase inhibitor first.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) 1) an effective date of the first Wednesday after a 90-day implementation period in all points of service (POS); and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 6, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Inhaled Corticosteroids/Long-Acting Beta Agonists (ICS/LABAs) Combinations

Background and Relative Clinical Effectiveness Conclusion—The P&T Committee evaluated the clinical effectiveness of the ICS/LABA combinations, which were last reviewed for UF

status in February 2009. Since the last review, one new drug, fluticasone/vilanterol (Breo Ellipta) has been marketed. Military Health System (MHS) expenditures for the class were $168 million in calendar year 2013. The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 0 absent) with the following conclusions:

1. Fluticasone/salmeterol (Advair) and budesonide/formoterol (Symbicort) are highly therapeutically interchangeable for asthma. For asthma, head-to-head trials and systematic reviews show no significant differences in efficacy.
2. For chronic obstructive pulmonary disease (COPD), there is insufficient evidence to conclude that there are clinically relevant differences in efficacy between Advair and Symbicort.
3. Advair Diskus, Symbicort, and Breo Ellipta are all FDA-approved for maintenance treatment of COPD; however, only Advair Diskus and Breo Ellipta are specifically approved for decreasing COPD exacerbations. Symbicort does have data from observational studies showing decreases in COPD exacerbations.
4. For mometasone/formoterol (Dulera), there are no head-to-head trials with another ICS/LABA in asthma; clinically relevant differences in efficacy are not expected. Dulera is not approved for COPD; two trials have shown benefit in improving spirometric endpoints in COPD.
5. There is only limited data for Breo Ellipta in patients with asthma, and it is not FDA-approved for this indication.
6. Breo Ellipta offers the convenience of once-a-day dosing in COPD. However, the long-term safety of the LABA component vilanterol is not known. One large trial (SUMMIT) evaluating mortality as a primary endpoint is underway.
7. Advair Diskus in the only drug approved for treatment of asthma in children down to the age of four years; however, for this age range, a metered dose inhaler (MDI) with a spacer is more commonly used. It also has the advantage of availability in both a MDI [Advair hydrofluoroalkane (HFA)] and dry powder inhaler (Advair Diskus).
8. For safety, a systematic review did not show clinically relevant differences between Advair and Symbicort in asthma. Advair Diskus, Advair HFA, Symbicort, Dulera, and Breo Ellipta all contain the same black box warnings and precautions. All drugs containing a LABA carry a black box warning for the increased risk of death in asthma.
9. Breo Ellipta and Dulera have a lower degree of interchangeability with Advair and Symbicort, due to their limited FDA-approved indications.
10. The Pharmacy Outcomes Research Team (PORT) presented an analysis of the use of ICS/LABAs by indications and found that asthma represents the majority of MHS use (67% of beneficiaries had ICD-9 diagnosis codes indicative of asthma, while 37% had codes for COPD, and 17% had codes for neither diagnosis). However, there was considerable overlap between the COPD and asthma diagnosis codes.

Relative Cost-Effectiveness Analysis and Conclusion—A pharmacoeconommic analysis and budget impact analysis (BIA) were performed to evaluate the ICS/LABAs. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

- The pharmacoeconomic analysis showed that fluticasone/salmeterol (Advair Diskus/Advair HFA) was the most cost-effective agent in this class, followed by mometasone/formoterol (Dulera), budesonide/formoterol (Symbicort), and fluticasone/salmeterol (Breo Ellipta).
- A BIA was performed to evaluate the potential impact of scenarios, with selected agents designated step-preferred and formulary or non-preferred and NF on the UF. BIA results showed that the scenario where Advair Diskus and Advair HFA are designated as step-preferred and formulary, with Dulera, Symbicort, and Breo Ellipta designated as non-preferred and NF, was the most cost-effective option for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following for the ICA/LABAs, based on clinical and cost effectiveness:
    - UF and step-preferred: fluticasone/salmeterol (Advair Diskus and Advair HFA)
    - NF and non-preferred: budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/vilanterol (Breo Ellipta)
    - This recommendation includes step therapy, which requires a trial of Advair Diskus or Advair HFA in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) that fluticasone/salmeterol (Advair Diskus and Advair HFA) remain on the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Symbicort, Dulera, and Breo Ellipta. (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) automated (step therapy) and manual PA criteria in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years of age; a trial of Advair Diskus or Advair HFA is required before the non-step preferred drugs.

5. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—QLs currently apply to the ICS/LABAs. The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) QLs for Advair Diskus, Advair HFA, Symbicort, Dulera, and Breo Ellipta of 1 inhaler/30 days in the Retail Network and 3 inhaler/90 days in the Mail Order Pharmacy.

6. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision; and, 3) that the ICS/LABA Drug Class be added to the safety net program (Rapid Response Program). Based on the P&T Committee's recommendation, the effective date is July 9, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Gastrointestinal-1 (GI-1s) Drug Class: Oral Aminosalicylates Subclass

Background and Relative Clinical Effectiveness Conclusion—The P&T Committee evaluated the relative clinical effectiveness of the oral aminosalicylates, a subclass within the GI-1s Drug Class. The subclass is comprised of generic sulfasalazine and the 5-aminosalicylate (5-ASA) products [balsalazide (generic Colazal and Giazo), olsalazine (Dipentum), and mesalamine (Delzicol, Asacol HD, Pentasa, Lialda, and Apriso)].

The GI-1s were previously reviewed for UF placement in February 2011, and mesalamine delayed release (DR) tablets (Asacol), along with generic sulfasalazine, were recommended for BCF addition. Asacol was discontinued from the market in March 2013 due to safety concerns of dibutyl phthalate (DBP) present in the enteric coating of Asacol tablets. A new phthalate-free mesalamine DR formulation, Delzicol is now available. At the May 2013 meeting, Asacol was removed from the BCF, pending a re-review of the subclass. Currently, the only aminosalicylate on the BCF is sulfasalazine.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the aminosalicylates drug class:

1. Sulfasalazine remains the first-line oral aminosalicylate. For the induction of remission in active ulcerative colitis (UC), evidence from two systematic reviews found no clinically relevant differences in efficacy between sulfasalazine and the newer 5-ASA formulations.

2. For maintenance of remission in UC, another systematic review showed a therapeutic advantage of sulfasalazine over the 5-ASA formulations. This advantage was offset by an increase in adverse events observed with sulfasalazine, due to the sulfapyridine moiety.
3. The newer 5-ASA formulations employ different release mechanisms, which deliver the active drug to various sites in the GI tract. These differences in drug release and site of release do not confer additional benefits in terms of clinical response.
4. The mesalamine product Delzicol is the phthalate-free replacement for Asacol that is bioequivalent to its predecessor; no clinical trials were conducted to evaluate efficacy or safety.
5. Giazo is a new balsalazide product with a higher strength per unit than the other balsalazide formulations (1,100 mg versus 750 mg with Colazal). It is not approved for use in women, and it offers no compelling advantage to the other balsalazide products commercially available.
6. The safety profile is similar for the 5-ASA products, based on systematic reviews. In clinical trials, females treated with Giazo reported more adverse events than males.
7. Lialda and Apriso are dosed once daily, which provides patient convenience, but have not been shown to have clinically relevant benefits in terms of adherence compared to 5-ASAs dosed twice or three times daily. Lialda and Apriso also have the lowest tablet burden.
8. The 5-ASA products are highly therapeutically interchangeable for treating UC. The choice of 5-ASA for UC will depend on other factors, such as location and extent of disease, as well as patient preference in terms of tablet burden and frequency of dosing.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed to evaluate the GI-1s Aminosalicylate Subclass. The P&T Committee concluded (15 for, 0 opposed, 1 abstained, 0 absent) the following:

- CMA results showed that generic sulfasalazine was the most cost-effective agent in this subclass, followed by balsalazide 750 mg (Colazal, generics), olsalazine (Dipentum), and the branded mesalamine agents Apriso, Lialda, Delzicol, Asacol HD, and Pentasa. Giazo (branded balsalazide 1,100 mg) was not cost-effective relative to other agents in this class.

- BIA was performed to evaluate the potential impact of scenarios with selected agents designated formulary or NF on the UF. BIA results showed the scenario with Apriso, Delzicol, and Lialda designated as formulary on the UF, with Asacol HD and Pentasa designated as NF, was the most cost-effective for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following, based on the high degree of therapeutic interchangeability and cost-effectiveness:

    - UF: sulfasalazine, balsalazide 750 mg (Colazal, generics), olsalazine (Dipentum), and the mesalamine products Delzicol, Lialda, and Apriso
    - NF: Pentasa, Asacol HD and the balsalazide 1,100 mg product (Giazo)

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) retaining sulfasalazine on the BCF, and adding mesalamine multimatrix (Lialda) to the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Pentasa, Asacol HD, and Giazo. (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 6, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Pancreatic Enzyme Products (PEPs)

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the PEPs. The class was previously an extended core formulary (ECF) class and last reviewed in February 2011. The PEPs were reviewed for the FDA-approved indication of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis or other conditions; other uses (e.g., pain relief from pancreatitis) were not reviewed. Since the last review, three new products, Pertzye, Viokace, and Ultresa, have been marketed. The PEPs all contain various amounts of lipase, amylase, and protease.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (15 for, 1 opposed, 0 abstained, 0 absent) the following conclusions:

1. Based on clinical efficacy alone, Creon, Pancreaze, Zenpep, Viokace, Ultresa, and Pertzye are effective at increasing coefficient of fat absorption in patients with EPI, compared to placebo. Only limited clinical trial data is available.
2. Creon has the most indications and highest MHS utilization. Among the PEPs, Creon has an additional indication for EPI due to pancreatitis or pancreatetcomy, without requiring use of a proton pump inhibitor.
3. Zenpep has the most dosage strengths available.
4. Zenpep and Viokace have information for gastrostomy tube administration.
5. Viokace is an uncoated tablet that is not approved for use in pediatrics; it requires administration with a proton pump inhibitor, to prevent degradation in the stomach.
6. Creon, Pancreaze, and Zenpep have dosing recommendations for infants as young as 12 months of age while Pancreaze has dosing information in infants as young as 6 months.
7. Pertzye and Ultresa have limited data regarding efficacy in treating EPI and have limited dosage strengths available.
8. With regards to safety, the available evidence suggests there are no clinically relevant differences between any of the PEPs.
9. There is a high degree of therapeutic interchangeability among the class.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed to evaluate the PEP Drug Class. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that Creon was the most cost-effective agent in this class, followed by Zenpep, Pancreaze, and Viokace. Ultresa and Pertzye were not cost-effective relative to other agents in this class.
- BIA was performed to evaluate the potential impact of scenarios with selected agents designated formulary or NF on the UF. BIA results showed the scenario with Creon, Zenpep, Pancreaze, and Viokace designated as formulary on the UF, with Ultresa and Pertzye designated as NF on the UF, was the most cost-effective for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (13 for, 2 opposed, 1 abstained, 0 absent) Creon, Pancreaze, Zenpep, and Viokace remain on the UF, and that Pertzye and Ultresa be designated as NF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) reclassifying the PEPs as a BCF class instead of an ECF class, and adding Creon to the BCF. As a result of this action, Pancreaze is removed from the ECF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Pertzye. (See Appendix B for the full MN criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is August 6, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VI. RE-EVALUATION OF NF AGENTS: DULOXETINE (CYMBALTA)

On an ongoing basis, the DHA Pharmacoeconomic Branch monitors changes in the clinical information, current costs, and utilization trends to determine whether the UF status of agents designated as NF needs to be readdressed. The P&T Committee's process for reevaluating NF agents was established at the May 2007 meeting and approved by the Director, TMA, on June 24, 2007.

The P&T Committee reevaluated the UF status of duloxetine (Cymbalta) in light of recent price reductions in generic formulations across all three POS. Additionally, automated PA (step therapy) requires a trial of a generic formulary antidepressant or generic non-opioid pain syndrome drug before receiving Cymbalta. As of the meeting, the generic duloxetine products were not cost-effective relative to the price of branded Cymbalta.

1. ***COMMITTEE ACTION: DULOXETINE UF RECOMMENDATION AND IMPLEMENTATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) maintaining Cymbalta as NF and continuing the current step therapy. When generic formulations of Cymbalta become cost-effective relative to the step-preferred agents, generic duloxetine will move to UF status, become step-preferred (e.g., "in front of the step"), and existing PA criteria will be removed without further action by the P&T Committee, Beneficiary Advisory

Panel, or Director, DHA. A generic agent is cost-effective relative to step-preferred agents when the generic agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the step-preferred agent.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VII. UTILIZATION MANAGEMENT

A. PAs

1. **Overactive Bladder (OAB) Drugs: Mirabegron (Myrbetriq)**—Mirabegron was FDA-approved for OAB in June 2012 and launched in October 2013. It will be reviewed as a new drug at an upcoming meeting. Mirabegron is a beta-3 agonist, which is a unique mechanism compared to the antimuscarinic OAB drugs (darifenacin, fesoterodine, tolterodine, oxybutynin, solifenacin, and trospium). In placebo-controlled trials, the efficacy of mirabegron on OAB symptoms appears similar to that of the other OAB drugs; however, mirabegron causes less anticholinergic AEs (dry mouth, constipation). The OAB drugs were reviewed for UF placement in November 2012, and automated PA (step therapy) was implemented, requiring a trial of a generic OAB drug or Detrol LA in all new and current users of an OAB drug.

   a) ***COMMITTEE ACTION: MIRABEGRON (MYRBETRIQ) PA CRITERIA***
   The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 1 absent) PA criteria for all new users of mirabegron (Myrbetriq) for OAB. (See Appendix C for full criteria.)

   b) ***COMMITTEE ACTION: MIRABEGRON (MYRBETRIQ) UF IMPLEMENTATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all POS. The effective date is June 11, 2014.

2. **Phosphodiesterase-5 (PDE-5) Inhibitor: Avanafil (Stendra)**—Avanafil is a new PDE-5 inhibitor approved by the FDA in April 2012, but not launched until January 2014. It is only approved for erectile dysfunction (ED). Currently, automated PA (step therapy) applies to the class for ED; Viagra is the step-preferred PDE-5 for ED.

   a) ***COMMITTEE ACTION: AVANAFIL (STENDRA) PA CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) PA

criteria for all users of Avanafil (Stendra) for ED. A trial of sildenafil (Viagra) for ED is required prior to using Stendra. Uses other than ED, including benign prostatic hypertrophy, following prostatectomy, pulmonary arterial hypertension, or Raynaud's phenomenon are not allowed. (See Appendix C for full criteria.)

B. QLs

1. **Hepatitis C Drugs: Sofosbuvir (Sovaldi)**—Sofosbuvir (Sovaldi) is a new direct acting agent for hepatitis C approved on December 18, 2013. QLs currently apply to the hepatitis C drugs, including the direct acting antiviral agents. Sofosbuvir efficacy was established in patients with genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma awaiting liver transplantation and those co-infected with HIV. It can be used without interferon in patients with genotype 1, 2, or 3 hepatitis C virus.

   a) ***COMMITTEE ACTION: SOFOSBUVIR (SOVALDI) QLs***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) QLs for sofosbuvir of 28 tablets per 28 days in all POS [Medical Treatment Facility (MTF), Retail Network, and Mail Order Pharmacy], consistent with the FDA-approved product dosing of one tablet given once daily.

2. **PDE-5 Inhibitors: Avanafil (Stendra)**—QLs currently apply to the PDE-5 inhibitors. The P&T Committee evaluated QLs for avanafil for treatment of ED.

   a) ***COMMITTEE ACTION: AVANAFIL (STENDRA) QLs***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) QLs for Avanafil of 6 tablets per 30 days in the Retail Network and 18 tablets for 90 days in the Mail Order Pharmacy, consistent with the other PDE-5 inhibitors. This is a collective QL, a maximum of 6 tablets (Retail Network) or 18 tablets (Mail Order Pharmacy) of any PDE-5 is allowed.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. OVERVIEWS

Overviews of the ICS and Nasal Allergy Drugs (nasal antihistamines, nasal corticosteroids, and nasal anticholinergics) drug classes were presented to the P&T Committee. The P&T

Committee provided expert opinion regarding those clinical outcomes considered most important for use in contract solicitation and for completing the clinical effectiveness review and developing the appropriate cost-effectiveness modes. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

IX. ITEMS FOR INFORMATION

A. **Medication Adherence**—The PORT updated the P&T Committee regarding progress in formulating a process and algorithm for measuring medication adherence. The algorithm is intended for use as a DHA quality measure and in coordination with the DHA Health Information Technology Branch for potential inclusion in the Population Health Portal as a practical tool for clinicians and clinic managers at point of care. The overall DHA metrics follow recommendations from the Pharmacy Quality Alliance/National Committee for Quality Assurance and will allow comparison to Center for Medicare Services Star Rating measures for health plans.

X. ADJOURNMENT

The meeting adjourned at 1650 hours on February 12, 2014. The next meeting will be in May 2014.

Appendix A—Attendance: February 2014 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix E—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

12 May 2014
Date

Appendix A—Attendance: February 2014 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
LTC Robert Conrad, MS	Chief, DHA Pharmacoeconomic Branch (Recorder)
COL John Spain, MS	Army, Pharmacy Officer
Col Scott Sprenger, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Derrik Clay for CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
LTC Dan Hsu for COL Ted Cieslak, MC	Army, Physician at Large
Col Michael Wynn, MC	Army, Family Practice Physician
LCDR Carey Welsh, MC	Navy, Pediatrics Physician
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Mr. Vincent Calebrese for Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Voting Members Absent	
Col Michael Spilker, BSC	DHA Deputy Chief, Pharmacy Operations Division
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, DHA
LT Col Dan Castiglia	Defense Logistics Agency Troop Support
LCDR Bob Selvester, MC	VA/DoD Evidence-Based Practice Guideline Work Group
CDR Brandon Hardin by phone	Medical Logistics Division, DLA

Appendix A—Attendance (continued)

Guests	
Mr. Bill Davies via DCO	Defense Health Agency, Pharmacy Operations Division
Capt Richard Caballero, via DCO	Defense Logistics Agency Troop Support
Mr. Alexander Quinones	Defense Logistics Agency Troop Support
CAPT Travis Watt	Vice Chair, IHS National P&T Committee
Others Present	
CAPT Walter Downs, MC	DHA Pharmacoeconomic Branch
LCDR Marisol Martinez, USPHS	DHA Pharmacoeconomic Branch
LCDR Joshua Devine, USPHS	DHA Pharmacoeconomic Branch
LCDR Linh Quach, MSC	DHA Pharmacoeconomic Branch
Maj David Folmar, BSC	DHA Pharmacoeconomic Branch
MAJ Misty Cowan, MC	DHA Pharmacoeconomic Branch
Dr. David Meade	DHA Pharmacoeconomic Branch
Dr. Angela Allerman	DHA Pharmacoeconomic Branch
Dr. Shana Trice	DHA Pharmacoeconomic Branch
Dr. Jeremy Briggs	DHA Pharmacoeconomic Branch
Dr. Brian Beck	DHA Pharmacoeconomic Branch
Dr. Amy Lugo via DCO	DHA Pharmacoeconomic Branch
Dr. Teresa Anekwe via DCO	DHA Pharmacy Operations Division
Ms. Deborah Garcia	DHA Pharmacoeconomic Branch contractor
Dr. Esmond Nwokeji	DoD Pharmacoeconomic Branch contractor
Mr. Kirk Stocker	DoD Pharmacoeconomic Branch contractor
Ms. Linda Paul	University of Incarnate Word, Feik School of Pharmacy student
Ms. Jennifer Miller via DCO	Lake Erie College of Osteopathic Medicine, School of Pharmacy student
Ms. Anna Humg via DCO	University of Maryland, School of Pharmacy student

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Budesonide/formoterol (Symbicort) • Mometasone/formoterol (Dulera) • Fluticasone/vilanterol (Breo Ellipta) **Inhaled Corticosteroids/ Long-Acting Beta Agonists (ICS/LABAs) Combinations**	• Use of Advair Diskus or Advair HFA is contraindicated • The patient has experienced or is likely to experience intolerable adverse effects to Advair Diskus or Advair HFA. • The patient has had an inadequate response to Advair Diskus or Advair HFA. • The patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk.
• Bupropion 450 mg XL (Forfivo XL) **Antidepressant-1s (AD-1s)**	• Use of formulary agents (bupropion, bupropion SR, bupropion XL) is contraindicated and treatment with other formulary antidepressants is not clinically appropriate. Provider must state why the patients cannot take generic bupropion, bupropion SR, or bupropion XL.
• desvenlafaxine ER (Khedezla) **Antidepressant-1s (AD-1s)**	• Use of the formulary agents venlafaxine IR or venlafaxine ER are contraindicated • The patient has experienced or likely to experience significant adverse effects from the formulary agents venlafaxine IR or venlafaxine ER. • Formulary agents resulted or are likely to result in therapeutic failure. • Patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk.
• Levomilnacipran (Fetzima) **Antidepressant-1s (AD-1s)**	• Use of formulary AD-1s are contraindicated • Patient has experienced or is likely to experience significant adverse effects from formulary AD-1s. • Formulary AD-1s resulted or are likely to result in therapeutic failure. • Patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk. • No alternative formulary agent **Formulary alternatives:** (selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitor (except milnacipran), tricyclic antidepressants, mirtazapine, bupropion, serotonin antagonist reuptake inhibitors, mononamine oxidase inhibitors)
• Brintellix (Vortioxetine) **Antidepressant-1s (AD-1s)**	• Use of formulary AD-1s are contraindicated • Patient has experienced or is likely to experience significant adverse effects from formulary AD-1s. • Formulary AD-1s resulted or are likely to result in therapeutic failure • Patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk • No alternative formulary agent **Formulary alternatives:** (selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitor (except milnacipran), tricyclic antidepressants, mirtazapine, bupropion, serotonin antagonist reuptake inhibitors, mononamine oxidase inhibitors)

Drug / Drug Class	Medical Necessity Criteria
• Balsalazide 1100 mg (Giazo) • Mesalamine high dose (Asacol HD) • Mesalamine (Pentasa) **Gastrointestinal-1 Drugs (GI-1s), aminosalicylates**	• Use of formulary oral aminosalicylates are contraindicated
• Pertzye • Ultresa **Pancreatic Enzyme Products (PEPs)**	• Use of formulary oral PEPs are contraindicated • No alternative formulary agent; patient requires a strength that is not available with the formulary PEPs

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Budesonide/formoterol (Symbicort) • Mometasone/formoterol (Dulera) • Fluticasone furoate/vilanterol (Breo Ellipta) **Inhaled Corticosteroids/Long-Acting Beta Agonists (ICS/LABAs) Combinations**	PA criteria apply to all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years of age. Automated PA criteria: The patient has filled a prescription for Advair or Advair HFA at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—Symbicort, Dulera, or Breo Ellipta is approved (e.g., trial of Advair Diskus or Advair HFA is NOT required) if: • Patient has experienced any of the following issues with either Advair Diskus or Advair HFA, which is not expected to occur with the non-preferred ICS/LABA combination drug: o inadequate response to Advair Diskus or Advair HFA o intolerable adverse effects o contraindication o patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk
• Desvenlafaxine ER (Khedezla) **Antidepressant1-s (AD-1s)**	PA criteria apply to all new users of Khedezla Automated PA criteria The patient has filled a prescription for venlafaxine IR or venlafaxine ER at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—If automated criteria are not met, Khedezla is approved in new users (e.g., trial of venlafaxine IR or venlafaxine ER is NOT required) if: • Use of the formulary SNRI (venlafaxine) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate. • The patient has previously responded to Khedezla, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Khedezla and changing to a formulary medication would present a risk of destabilization). • The patient is being treated for depression, requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has failed an adequate trial of venlafaxine. Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit. • The patient requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has been unable to tolerate venlafaxine.

• Levomilnacipran (Fetzima) **Antidepressant1-s (AD-1s)**	PA criteria apply to all new users of Fetzima. Automated PA criteria • The patient has filled a prescription for a formulary SSRI, duloxetine, SNRIs (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or an MAOI at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—For new users, Fetzima is approved (e.g., trial of a formulary AD-1 listed above is NOT required) if: • Use of a formulary antidepressant (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate. • The patient has previously responded to Fetzima, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Fetzima and changing to a formulary medication would present a risk of destabilization). • The patient is being treated for depression and has failed therapy with the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI). Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit. • The patient is being treated for depression and has been unable to tolerate the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI).

Drug / Drug Class	Prior Authorization Criteria
• Vortioxetine (Brintellix) **Antidepressant1-s (AD-1s)**	PA criteria apply to all new users of Brintellix. <u>Automated PA criteria</u> • The patient has filled a prescription for a formulary SSRI, duloxetine, SNRIs (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or an MAOI at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND <u>Manual PA criteria</u>—For new users, Brintellix is approved (e.g., trial of a formulary AD-1 listed above is NOT required) if: • Use of a formulary antidepressant (SSRI, duloxetine, SNRI except milnacipran, TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate. • The patient has previously responded to Brintellix, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Brintellix and changing to a formulary medication would present a risk of destabilization). • The patient is being treated for depression and has failed therapy with the formulary antidepressants (SSRI, duloxetine, SNRI except milnacipran, TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI). Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit. • The patient is being treated for depression and has been unable to tolerate the formulary antidepressants (SSRI, duloxetine, SNRI except milnacipran, TCA, mirtazapine, bupropion, trazodone or nefazodone, or, MAOI).

Drug / Drug Class	Prior Authorization Criteria
• Mirabegron (Myrbetriq) **Overactive Bladder (OAB) Drugs**	PA criteria apply to all new users of Myrbetriq Automated PA criteria • The patient has filled a prescription for tolterodine ER (Detrol LA), oxybutynin ER, oxybutynin IR, or generic trospium IR (Sanctuary) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. Manual PA criteria—If automated criteria are not met, Myrbetriq is approved if: • Coverage is only approved for the FDA-approved indication of OAB with symptoms of urge incontinence, urgency, and urinary frequency • Patient has failed a 12-week trial with at least one of the following step-preferred OAB drugs (Detrol LA, oxybutynin ER, oxybutynin IR, or trospium IR) due to a treatment failure or intolerable adverse effects. • Patient has experienced central nervous system (CNS) adverse effects with oral OAB medications or is at increased risk for such CNS effects due to comorbid conditions or other medications.
• Avanafil (Stendra) **Phosphodiesteraise-5 (PDE-5) Inhibitor**	PA applies to all new and current users of avanafil (Stendra). Automated PA criteria • The patient has received a prescription for sildenafil (Viagra) at any MHS point of service (MTFS, Retail Network or Mail Order) during the previous 180 days. • The patient is a male, aged 40 years of older with ED. Manual PA criteria—if automated criteria are not met. Stendra is approved if • The patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects. • Treatment with Viagra is contraindicated. Note: Coverage is approved only for erectile dysfunction (ED). Use for benign prostatic hyperplasia (BPH), following prostatectomy, pulmonary arterial hypertension, and Raynaud's phenomenon is not allowed. Additionally, use is not allowed for treatment of ED in males younger than age 18, for ED due to psychogenic origin, or in women for female sexual dysfunction.

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2014	**Inhaled Corticosteroids/ Long-Acting Beta Agonists (ICS/LABAs) Combinations**	UF class review Previously reviewed	▪ Fluticasone/ salmeterol (Advair Diskus) ▪ Fluticasone/ salmeterol (Advair HFA)	▪ None (Advair Diskus and Advair HFA BCF)	▪ Budesonide/formoterol (Symbicort) ▪ Mometasone/formoterol (Dulera) ▪ Fluticasone/vilanterol (Breo Ellipta)	Pending singing of the minutes / 60 days	▪ Step therapy required; see comments ▪ Quantity Limits apply; see Minutes	▪ Must try Advair before Symbicort, Dulera, or Breo Ellipta in all current and new users older than 12 years. (See Appendix C)
Feb 2014	**GI-1s** **5-Amino Salicylate Subclass**	UF Class review Previously reviewed	▪ Sulfasalazine ▪ Mesalamine multimatrix (Lialda)	▪ Balsalazide 750 mg (Colazal, generic) ▪ Olsalazine (Dipentum) ▪ Mesalamine DR (Delzicol) ▪ Mesalamine (Apriso)	▪ Balsalazide 1100 mg (Giazo) ▪ Mesalamine high dose (Asacol HD) ▪ Mesalamine (Pentasa)	Pending signing of the minutes / 90 days	▪ None	▪ None
Feb 2014	**Pancreatic Enzyme Products (PEPs)**	UF class review	▪ Creon	▪ Pancreaze ▪ Viokace ▪ Zenpep	▪ Pertzye ▪ Ultresa	Pending signing of the minutes / 90 days	▪ None	▪ Note Pancreaze removed from the ECF.

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2014	**Depression and Non-Opioid Pain Syndrome Agents** **Antidepressant-1s Subclass** Previous review: Aug 2011	New Drug in Already Reviewed Class Bupropion 450 mg (Forfivo XL) Desvenlafax-ine ER (Khedezla) Levomilnaci-pran (Fetzima) Vortioxetine (Brintellix)	No change from previous review **SSRIs:** citalopram fluoxetine sertaline **SNRIs:** venlafaxine IR venlafaxine ER **SARIs:** trazodone **NDRIs:** bupropion HCl IR bupropion HCl SR bupropion HCl ER **GABA analogs:** gabapentin **TCAs:** amitriptyline doxepin imipramine HCl nortriptyline	**SSRIs:** citalopram fluoxetine escitalopram fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate sertraline **SNRIs:** venlafaxine IR venlafaxine ER venlafaxine ER tablets **SARIs:** nefazodone trazodone **NDRIs:** bupropion HCl IR bupropion HCl SR bupropion HCl ER **TCAs:** amitriptyline desipramine doxepin imipramine HCl imipramine pamoate nortriptyline protriptyline **A2RAs:** mirtazapine tablets mirtazapine ODT **GABA analogs:** gabapentin	*Feb 2014* ▪ **bupropion 450 mg (Forfivo XL)** ▪ **desvenlafaxine ER (Khedezla)** ▪ **levomilnacipran (Fetzima)** ▪ **vortioxetine (Brintellix)** *Nov 2011* **SSRIs:** fluoexetine (Sarafem) fluoxetine weekly (Prozac Weekly) **SNRIs:** desvenlafaxine (Pristiq) duloxetine (Cymbalta) milnacipran (Savella) **SARIs:** trazodone ER (Oleptro) **SPARIs:** vilazodone (Viibryd) **NDRIs:** bupropion HBr (Aplenzin) **GABA analogs:** pregabalin (Lyrica)	Pending signing of minutes/ 90 days	Step therapy required; see comments	▪ Khedezla: Must try venlafaxine IR or ER first ▪ Fetzima and Brintellix: Must try a formulary AD-1 first. (See Appendix C)

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix E—Table of Abbreviations

5-ASA	5-aminosalicylate
AD-1s	Antidepressants Drug Class
AEs	adverse events
BCF	Basic Core Formulary
BIA	budget impact analysis
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DBP	dibutyl phthalate
DCO	Defense Connect Online
DHA	Defense Health Agency
DoD	Department of Defense
DR	delayed release
ED	erectile dysfunction
EPI	exocrine pancreatic insufficiency
ER	extended release
FDA	U.S. Food and Drug Administration
GI-1s	Gastrointestinal-1 Drug Class
HAMD	Hamilton Depression Rating Scale
HFA	hydrofluoroalkane
ICS/LABAs	Inhaled Corticosteroids/Long-Acting Beta Agonists Drug Class
IR	immediate release
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	mononamine oxidase inhibitor
MDD	major depressive disorder
MDIs	metered-dose inhalers
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NDRI	norepinephrine/dopamine reuptake inhibitor
NF	nonformulary
OAB	overactive bladder
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE-5	phosphodiesterase-5 inhibitor
PEPs	Pancreatic Enzyme Products
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
SARIs	serotonin antagonist reuptake inhibitor
SNRI	serotonin/norepinephrine reuptake inhibitor
SSRIs	serotonin reuptake inhibitors
UC	ulcerative colitis
UF	Uniform Formulary
XL	extended release

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INTERIM MEETING

Addendum December 17, 2013

I. UNIFORM FORMULARY (UF) DRUG CLASS REVIEWS

A. Anti-Lipidemic-1s (LIP-1s)

Background—New lipid treatment guidelines were released on November 12, 2013, one day prior to the November Department of Defense (DoD) Pharmacy & Therapeutics (P&T) Committee meeting. An interim meeting was held to determine the clinical and cost-effectiveness, and UF status of the LIP-1 drugs, based on the new guidelines (found at http://content.onlinejacc.org/article.aspx?articleID=1770217). Military Treatment Facilities (MTFs) and Managed Care Support Contractors were surveyed on their opinions of the new guidelines and potential changes in statin prescribing in the Military Health System (MHS).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 3 absent) the following clinical effectiveness conclusions:

- New lipid guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) released on November 12, 2013, recommend statin therapy for patients in the following four risk categories:
  - With clinical atherosclerotic cardiovascular disease (ASCVD)
  - Low-density lipoprotein (LDL) cholesterol ≥190 mg/dL
  - Type 2 diabetic mellitus patients age 40–75 without ASCVD and with LDL between 70–189 mg/dL
  - Patients age 40–75 with 10-year cardiovascular (CV) CV risk ≥7.5% and LDL between 70–189 mg/dL but without history of ASCVD
- Based on the four risk groups, the number of patients eligible to receive statin therapy will likely increase.
- A new risk assessment scoring tool based on gender, race, age, total cholesterol, and LDL is now recommended.
- Other changes from the previous Adult Treatment Panel 3 guideline are that treatment targets based on LDL or high-density lipoprotein (HDL) are no longer recommended, dose titration based on LDL is not recommended, and there is no differentiation in statins in terms of primary and secondary prevention.
- Statins are categorized into three groups—
  - High intensity (LDL lowering ≥50%): atorvastatin 40 mg, 80 mg; rosuvastatin (Crestor) 20 mg, 40 mg

- Moderate intensity (LDL lowering between 30% to <50%): atorvastatin 10 mg, 20 mg; rosuvastatin (Crestor) 5 mg, 10 mg; simvastatin 20 mg, 40 mg; pravastatin 40 mg, 80 mg; lovastatin 40 mg; fluvastatin ER (Lescol XL) 80 mg; fluvastatin 40 mg twice daily; pitavastatin (Livalo) 2 mg, 4 mg
- Low intensity (LDL lowering <30%): simvastatin 10 mg; pravastatin 10 mg, 20 mg; lovastatin 20 mg; fluvastatin 20 mg, 40 mg; pitavastatin (Livalo) 1 mg

- Non-statin therapies (ezetimibe, niacin, fibrates, bile acid salts), whether alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.
- Non-statin therapies can be considered for patients who experience adverse events from statins, less than anticipated responses, those with statin tolerability issues, or those with drug interactions.
- Based on the current guidelines, and to meet the needs of DoD beneficiaries, at least one statin from each of the statin intensity groups (low, moderate, and high intensity) is required on the Uniform Formulary.

Relative Cost-Effectiveness—Cost-effectiveness analysis (CEA) and budget impact analysis (BIA) were performed for the LIP-1s. For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted. The CEA was based in part on evidence and efficacy outcomes published in the 2013 ACC/AHA lipid guidelines. The CEA assessed LIP-1s based on the efficacy (i.e., intensity) of statin therapy, according to the average expected LDL lowering from low-, moderate-, or high-intensity statins. The CEA evaluated the following:

- statin monotherapy agents: atorvastatin, fluvastatin, fluvastatin ER (Lescol XL), lovastatin, lovastatin ER (Altoprev), pitavastatin (Livalo), pravastatin, rosuvastatin (Crestor), and simvastatin; and,
- fixed-dose combination therapy agents: amlodipine/atorvastatin, ezetimibe/atorvastatin (Liptruzet), ezetimibe/simvastatin (Vytorin), niacin/lovastatin (Advicor), and niacin/simvastatin (Simcor).

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 3 absent) the following:

- For low-intensity statins, generic simvastatin was the most cost-effective of this subgroup of drugs, based on the weighted average cost per day of treatment across all three points of service, followed by lovastatin, pravastatin, fluvastatin, and pitavastatin (Livalo) (ranked in order from most to least cost-effectiveness)
- For moderate-intensity statins, generic simvastatin was the most cost-effective agent in this subgroup of drugs followed by generic atorvastatin 10 mg and 20 mg, lovastatin, pravastatin, rosuvastatin (Crestor) 5 mg and 10 mg, fluvastatin,

pitavastatin (Livalo), amlodipine/atorvastatin, fluvastatin ER (Lescol XL), and lovastatin ER (Altoprev).

- For high-intensity statins, generic atorvastatin 40 mg and 80 mg was the most cost-effective of this subgroup of drugs, followed by rosuvastatin (Crestor) 20 mg and 40 mg.
- For branded fixed-dose combination agents, cost analysis results showed ezetimibe/simvastatin (Vytorin) to have the lowest average cost per day in this subgroup, followed by ezetimibe/atorvastatin (Liptruzet), niacin/lovastatin (Advicor), and niacin/simvastatin (Simcor).
- Among the formulary options examined, CEA and BIA results showed the most cost-effective scenario designated all generic statins UF and step-preferred, with rosuvastatin (Crestor) as the formulary non-preferred agent (all new users required to try generic statins with equivalent intensity), and all other branded statin agents with nonformulary (NF) status and non-preferred.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 1 opposed, 0 abstained, 3 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS:
    - atorvastatin, atorvastatin/amlodipine, simvastatin, pravastatin, fluvastatin, and lovastatin be designated UF and step-preferred (e.g., "in front of the step");
    - rosuvastatin remain designated UF and non step-preferred (e.g., "behind the step"); and,
    - atorvastatin/ezetimibe (Liptruzet), simvastatin/ezetimibe (Vytorin), pitavastatin (Livalo), fluvastatin ER (Lescol XL), lovastatin ER (Altoprev), lovastatin/niacin (Advicor), and simvastatin/niacin (Simcor) be designated NF and non step-preferred (e.g., "behind the step").
    - This recommendation includes step therapy, which requires a trial of a generic statin at similar LDL-lowering intensity in new users of rosuvastatin (Crestor) 20mg and 40 mg and the NF statins, and manual PA criteria for new users of rosuvastatin 5 mg and 10 mg.

    Note that this recommendation does not affect the formulary status of ezetimibe (Zetia) or niacin ER (Niaspan). Ezetimibe remains UF and non step-preferred and Niaspan remains on the Basic Core Formulary (BCF).

    MTF pharmacies are highly encouraged to switch patients currently receiving Vytorin to statin monotherapy at the appropriate LDL-lowering intensity.

    MTFs are also encouraged to reserve new prescriptions for Crestor 20 mg or 40 mg for patients who are unable to tolerate atorvastatin 40 mg or 80 mg, and to consider a generic statin at the equivalent LDL-lowering intensity for new prescriptions, instead of Crestor 5 mg or 10 mg.

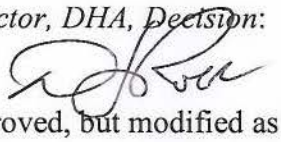
2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) maintaining simvastatin 10 mg, 20 mg, and 40 mg; atorvastatin; and, pravastatin on the BCF. Simvastatin 80 mg remains UF.

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) MN criteria for atorvastatin/ezetimibe (Litptruzet), simvastatin/ezetimibe (Vytorin), pitavastatin (Livalo), fluvastatin ER (Lescol XL), lovastatin ER (Altoprev), lovastatin/niacin (Advicor), and simvastatin/niacin (Simcor). (See Appendix B for full criteria.)

4. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) automated PA criteria (step therapy) and manual PA criteria for new users of rosuvastatin (Crestor) 20 mg and 40 mg, simvastatin/ezetimibe (Vytorin), atorvastatin/ezetimibe (Liptruzet), pitavastatin (Livalo), fluvastatin ER (Lescol XL), lovastatin ER (Altoprev), lovastatin/niacin (Advicor), and (simvastatin/niacin) Simcor, requiring a trial of a step-preferred statin with similar LDL-lowering intensity. The P&T Committee also recommended (11 for, 1 opposed, 1 abstained, 3 absent) manual PA criteria for new users of rosuvastatin (Crestor) 5 mg and 10 mg, requiring a trial of atorvastatin, simvastatin, and pravastatin. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; 2) DHA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved



Approved, but modified as follows:

II. UTILIZATION MANAGEMENT

A. MONTELUKAST (SINGULAIR) PA—PA criteria were recommended at the August 2011 meeting for montelukast (Singular), requiring automated PA criteria in patients with asthma, and requiring manual PA criteria for patients with seasonal allergic rhinitis or nasal polyps, based on professional treatment guidelines and cost. Generic montelukast tablets entered the market in August 2012 and, as of November 2013, there has been a significant decrease in the generic cost.

1. ***COMMITTEE ACTION: MONTELUKAST (SINGULAIR) PA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the PA requirements for montelukast be removed, effective upon signing of the minutes.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

III. SECTION 716 NATIONAL DEFENSE AUTHORIZATION ACT FISCAL YEAR 2013 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM

A. Section 716 Revised Manual PA Criteria—After the November 2013 DoD P&T Committee meeting, the Interim Final Rule for the Section 716 Maintenance Medication Program was published in the Federal Register (http://www.gpo.gov/fdsys/pkg/FR-2013-12-11/pdf/2013-29434.pdf.) The Rule is effective February 14, 2014. PA criteria were recommended at the November 2013 DoD P&T Committee meeting.

1. ***COMMITTEE ACTION: SECTION 716 MANUAL PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) revising the manual PA criteria for maintenance medications for the following circumstances:

    a) Patient has barriers to receiving medications by mail (e.g., no permanent address, resides in rural setting).

    b) Patient is not on a stable dose of medication; the medication is currently being titrated.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

10 Feb 2014
Date

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Atorvastatin/ezetimibe (Liptruzet) • Simvastatin/ezetimibe (Vytorin) **Antilipidemic-1s**	• There is no alternative formulary agent: the patient requires high-intensity statin therapy (LDL lowering >50%) or moderate-intensity statin therapy (LDL lowering between 30%–50% for Vytorin 10/10 mg) and is receiving ezetimibe and atorvastatin or simvastatin therapy separately and has swallowing difficulties, requiring use of the fixed-dose combination.
• Fluvastatin ER (Lescol XL) • Pitavastatin (Livalo) **Antilipidemic-1s**	• Use of the formulary statins is contraindicated and the patient cannot take pravastatin. • The patient has experienced or likely to experience significant adverse effects from the formulary statins.
• Lovastatin ER (Altoprev) **Antilipidemic-1s**	• There is no alternative formulary agent; the patient requires treatment with lovastatin 60 mg.
• Lovastatin/niacin (Advicor) • Simvastatin/niacin (Simcor) **Antilipidemic-1s**	• There is no alternative formulary agent; the patient is receiving Niaspan and lovastatin or simvastatin separately, and has swallowing difficulties, requiring use of the fixed-dose combination.

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Rosuvastatin (Crestor) 20 mg, 40 mg **Antilipidemic1-s (LIP-1s)**	All current users of Crestor are exempt from the PA criteria ("grandfathered"). New users of Crestor 20 mg, 40 mg must try a preferred statin at appropriate LDL lowering first. <u>Automated PA criteria</u> • The patient has filled a prescription for a preferred statin targeting similar LDL lowering >50% (generic atorvastatin 40 mg or 80 mg), at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND <u>Manual PA criteria</u>—If automated criteria are not met, Crestor 20 mg, 40 mg is approved in new users (e.g., trial of atorvastatin 40 mg, 80 mg is NOT required) if: • The patient requires a high-intensity statin (LDL lowering >50%) and has tried atorvastatin 40 mg or 80 mg and was unable to tolerate treatment due to adverse effects. • The patient requires a high-intensity statin (LDL lowering >50%) and is on a concurrent drug metabolized by the cytochrome p450 3A4 pathway.

• Rosuvastatin (Crestor) 5 mg, 10 mg **Antilipidemic1-s (LIP-1s)**	All current users of Crestor are exempt from the PA criteria ("grandfathered"). New users of Crestor 5 mg, 10 mg must try a preferred statin at appropriate LDL lowering first. <u>Manual PA criteria</u>—For new users, Crestor 5 mg or 10 mg is approved (e.g., trial of a generic statin at appropriate LDL lowering is NOT required) if: • The patient is taking a concurrent drug that is metabolized by CYP3A4 and cannot take pravastatin. The provider must state why the patient cannot take pravastatin. • The patient requires moderate LDL lowering (LDL decrease by 30% to 50%), and has tried all 3 of the following drugs: atorvastatin ≥10 mg, simvastatin ≥20 mg, and pravastatin ≥40 mg and could not tolerate treatment due to adverse effects. • Note that the previous requirements for step therapy are removed; all new users of Crestor 5 mg and 10 mg must have a manual ("hard copy") PA.
• Atorvastatin/ezetimibe (Liptruzet) • Simvastatin/ezetimibe (Vytorin) • Fluvastatin ER (Lescol XL) • Lovastatin ER (Altoprev) • Pitavastatin (Livalo) • Lovastatin/niacin (Advicor) • Simvastatin/niacin (Simcor) **Antilipidemic1-s (LIP-1s)**	All new users of Liptruzet, Vytorin, Lescol XL, Livalo, Altoprev, Advicor, and Simcor must try a preferred statin at appropriate LDL lowering first. <u>Automated PA criteria</u> • The patient has received a prescription for a preferred agent (generic atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, or pravastatin) targeting similar LDL reduction (LDL lowering <50%, LDL lowering between 30% to 50%, LDL lowering <30%) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND <u>Manual PA criteria</u>—If automated criteria are not met, Liptruzet, Vytorin, Lescol XL, Livalo, Altoprev, Advicor, and Simcor is approved (e.g., trial of generic statin is NOT required) if: • For Vytorin: The patient requires a high-intensity statin and

Drug / Drug Class	Prior Authorization Criteria
	has tried atorvastatin ≥40 mg and was unable to tolerate treatment due to adverse effects. • For Vytorin or Liptruzet: The patient requires high-intensity therapy and is receiving ezetimibe and atorvastatin or simvastatin separately, and has swallowing difficulties (needs a fixed-dose combination product). • For Livalo, Lescol XL: o The patient has tried a preferred statin with similar LDL reduction (moderate or low intensity) and was unable to tolerate it due to adverse effects. o The patient is taking a drug that is metabolized by CYP3A4 . • For Altoprev: The patient requires treatment with lovastatin 60 mg and cannot take another statin with similar LDL lowering. • For Simcor, Advicor: The patient requires a drug that lowers LDL and raises HDL and cannot take two separate tablets (needs fixed-dose combination).

Appendix G—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Dec 2013 Interim Meeting	**Antilipdemic-1s**	UF Class review Previously reviewed	▪ atorvastatin ▪ pravastatin ▪ simvastatin 10, 20, & 40 mg	▪ atorvastatin/amlodipine ▪ fluvastatin ▪ lovastatin ▪ simvastatin 80 mg ▪ rosuvastatin (Crestor) – non-step preferred – see comments	▪ simvastatin/ezetimibe (Vytorin) ▪ atorvastatin/ezetimibe (Liptruzet) ▪ fluvastatin ER (Lescol XL) ▪ lovastatin ER (Altoprev) ▪ pitavastatin (Livalo) ▪ lovastatin/niacin (Advicor) ▪ simvastatin/niacin (Simcor)	Pending signing of the minutes / 60 days	PA applies – see comments and Appendix C	▪ Step therapy applies to new users of Crestor and the 7 nonformulary drugs ▪ Current Crestor users are grandfathered (exempt from PA process) ▪ See Appendix C for details

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix H—Table of Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ASCVD	atherosclerotic cardiovascular disease
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CV	cardiovascular
DoD	Department of Defense
ER	extended release
HDL	high-density lipoprotein cholesterol
LDL	low-density lipoprotein cholesterol
LIP-1s	Antilipidemic-1s Drug Class
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
P&T	Pharmacy & Therapeutics
PA	prior authorization
UF	Uniform Formulary

DECISION PAPER

DEPARMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2013

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors—Alogliptin (Nesina), Alogliptin/Metformin (Kazano), and Alogliptin/Pioglitazone (Oseni)

Relative Clinical Effectiveness Conclusion—Alogliptin (Nesina) is the fourth DPP-4 inhibitor to reach the market. The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that alogliptin exhibits similar lowering of hemoglobin A1c as the other DPP-4 inhibitors and has a similar safety profile. Although alogliptin is the only DPP-4 available in a fixed-dose combination with thiazolidinedione, it offers no additional clinical benefits, as alogliptin requires renal dosing, and the multiple tablets strengths available may limit use.

Relative Cost-Effectiveness Conclusion—A cost minimization analysis (CMA) was performed. Based on the CMA results, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni) are more costly than the current Uniform Formulary (linagliptin products), Basic Core Formulary (sitagliptin products), and Nonformulary (saxagliptin products) DPP-4-inhibitors.

1. ***COMMITTEE ACTION: UNIFORM FORMULARY (UF) RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following:

   - alogliptin (Nesina), aloglptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni) be designated nonformulary (NF) and non-preferred.

   - This recommendation includes step therapy, which requires a trial of a sitagliptin product (Januvia, Janumet, Janumet XR) (the preferred drugs) prior to using the other DPP4-inhibitors. Prior authorization for the DPP-4 inhibitors also requires a trial of metformin or sulfonylurea for new patients.

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
Existing automated PA (step therapy) requires a trial of metformin or a sulfonylurea prior to use of a DPP-4 inhibitor. Additionally, sitagliptin-containing products (Januvia, Janumet, Janumet XR) are the preferred agents in the DPP-4 inhibitors subclass. New users must try a preferred sitagliptin product before trying linagliptin or saxagliptin-containing products. Juvisync has been voluntarily discontinued from the market as of October 2013, and will no longer be a preferred sitagliptin product on the UF.

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) PA criteria should apply to alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni). (See Appendix C for the full criteria.)

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS); and, 2) the Defense Health Agency (DHA) send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Osteoporosis Drugs—Bisphosphonate Subclass: Alendronate Effervescent Tablet (Binosto)

Relative Clinical Effectiveness Conclusion—Effervescent alendronate (Binosto) is a new effervescent formulation of alendronate (Fosamax, generics). The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 2 absent) that although Binosto may be more convenient for patients by requiring less consumption of water and to those patients with swallowing difficulties, there is no data that Binosto is better tolerated or safer than other alendronate formulations. The high sodium content with Binosto is a disadvantage over other alendronate formulations. Binosto offers no clinically compelling advantages over current formulary bisphosphonate agents.

Relative Cost-Effectiveness Conclusion—CMA was performed. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) effervescent alendronate (Binosto) is the least cost-effective oral bisphosphonate compared to current UF agents.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) effervescent alendronate (Binosto) be designated NF.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for effervescent alendronate (Binosto). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

II. UF DRUG CLASS REVIEWS

A. Short-Acting Beta Agonists (SABAs) Metered Dose Inhalers (MDIs)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that in terms of clinical effectiveness, there is little evidence to suggest there are clinically relevant differences between the albuterol hydrofluoroalkane (HFA) products (ProAir HFA, Proventil HFA, Ventolin HFA) and levalbuterol (Xoponex HFA) for their FDA approved indications. No new clinical conclusions were found since the previous review in November 2011. ProAir HFA now includes a dose counter. In order to meet the needs of Military Health System (MHS) patients, only one SABA is needed on the Basic Core Formulary (BCF).

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 3 absent) that among SABA HFA inhalers, ProAir HFA was the most cost-effective agent based on the weighted average cost per day of treatment across all three POS, followed by Xopenex HFA, Ventolin HFA, and Proventil HFA. Results from the CMA and budget impact analysis (BIA) showed that designating ProAir HFA as the sole UF agent in this class, with all other SABA HFA metered dose inhaler (MDIs) designated as NF, was the most cost-effective scenario for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) that ProAir HFA remain designated formulary on the UF. The P&T Committee also recommended that Proventil HFA, Ventolin HFA, and Xopenex HFA be designated NF on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) that ProAir HFA should be added to the BCF and Ventolin HFA should be removed from the BCF. The P&T Committee also recommended that local Military Treatment Facility (MTF) P&T Committees rapidly convert patients to ProAir HFA and provide patient education on proper inhaler technique.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) MN criteria for Proventil HFA, Ventolin HFA, and Xopenex HFA. (See Appendix B for full criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is May 14, 2014.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Benign Prostatic Hyperplasia Agents—5-Alpha Reductase Inhibitors (5-ARIs) Subclass

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following for the 5-ARIs:

- Finasteride and dutasteride (Avodart) appear interchangeable with regard to efficacy in treating lower urinary tract symptoms associated with benign prostatic hypertrophy (BPH). Both agents result in similar decreases in prostate volume, increases in urinary flow rate, and improvement in symptoms. Similar reductions in risk of acute urinary retention and BPH-related surgery are seen with both agents.

- Finasteride and dutasteride (Avodart) exhibit a high degree of therapeutic interchangeability. Either finasteride or dutasteride is expected to meet the needs of the majority of patients in the MHS who have BPH. Neither drug offers a unique benefit. It is unlikely that a patient who did not have an adequate response with one 5-ARI would have an improved response with the other.
- The combination product dutasteride/tamsulosin (Jalyn) confers no additional benefit when compared with using the individual components together. As the 5-ARIs are highly interchangeable, it likely makes little clinical difference which 5-ARI is used in combination with an alpha-1 blocker.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that the most cost-effective scenario designated finasteride (Proscar, generic) with formulary status on the UF, with dutasteride (Avodart) and dutasteride/tamsulosin (Jalyn) designated NF on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent,) the following:
    - finasteride (Proscar, generic) remain designated as formulary on the UF; and,
    - dutasteride (Avodart) and dutasteride/tamsulosin (Jalyn) be designated NF on the UF.
    - This recommendation includes step therapy, which requires a trial of a finasteride prior to using dutasteride (Avodart) in all current and new patients, or dutasteride/tamsulosin (Jalyn) in new users.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T recommended (15 for, 0 opposed, 1 abstained, 0 absent) finasteride remain designated as the BCF 5-ARI product.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) MN criteria for dutasteride (Avodart) and dutasteride/tamsulosin (Jalyn). (See Appendix B for the full criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***— The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) PA criteria should apply to the nonformulary 5-ARIs. A trial of finasteride is required prior to using dutasteride (Avodart) in all current and new patients, or dutasteride/tamsulosin (Jalyn) in all

new users. With the new requirement for use of finasteride prior to using Jalyn, the previous prior authorization criteria where a trial of alfuzosin or tamsulosin was required no longer apply. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, 0 abstained, 4 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

III. UTILIZATION MANAGEMENT

A. PAs

1. **Multiple Sclerosis (MS) Drugs: Dimethyl Fumarate (Tecfidera)**—Dimethyl fumarate is an oral disease modifying drug for MS that was FDA-approved in March 2013. The drug has not yet been reviewed for UF status. The package insert recommends measuring the complete blood count (CBC) within six months prior to initiation of therapy, due to the risk of lymphopenia. PA criteria apply to the other MS drugs.

    a) ***COMMITTEE ACTION: DIMETHYL FUMARATE (TECFIDERA) PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for dimethyl fumarate (Tecfidera) for relapsing forms of MS, and CBC monitoring, consistent with the product labeling. (See Appendix C for full criteria.)

2. **Targeted Immunomodulatory Biologics (TIBs): Certolizumab (Cimzia), Tocilizumab (Actemra), and Ustekinumab (Stelara)**—PA criteria currently apply to the TIBs. Tocilizumab was previously limited to injection by health care professionals, but is now available in pre-filled syringes labeled for patient self administration for treatment of rheumatoid arthritis. The FDA recently approved new indications for certolizumab for treatment of ankylosing spondylitis (AS) and psoriatic arthritis (PsA), and ustekinumab for treatment of PsA.

a) ***COMMITTEE ACTION: CERTOLIZUMAB (CIMZIA), TOCILIZUMAB (ACTEMRA), AND USTEKINUMAB (STELARA) PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for certolizumab for AS and PsA, tocilizumab for rheumatoid arthritis, and ustekinumab for PsA, consistent with the products' labeling. (See Appendix C for full criteria.)

B. Quantity Limits (QLs)

1. **TIB: Tocilizumab (Actemra)**—QLs currently apply to the TIBs. The P&T Committee evaluated QLs for tocilizumab for treatment of rheumatoid arthritis.

   a) ***COMMITTEE ACTION: TOCILIZUMAB (ACTEMRA) QLs***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) QLs for Actemra (162 mg/0.9 mL), limiting use to 4 pre-filled syringes per 28 days in the Retail Network, and 8 pre-filled syringes per 56 days via Mail Order, consistent with FDA-approved product labeling.

C. Copayment Change

1. **Niacin ER (Niaspan)**—The P&T Committee reviewed pricing for niacin ER (Niaspan). AB-rated generics are available for this product, but the branded product has significantly lower pricing.

   a) ***COMMITTEE ACTION: COPAYMENT CHANGE***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the Tier 1 copayment be assigned for Niaspan.

   b) ***COMMITTEE ACTION: COPAYMENT IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the Tier 1 copayment change for Niaspan become effective upon signing of the minutes.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

IV. FY2008 NATIONAL DEFENSE AUTHORIZATION ACT, SECTION 703

A. **Section 703**—The P&T Committee reviewed drugs from manufacturers that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not compliant with FY2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the Retail POS and medical necessity in MTFs. These NF drugs will remain available in the Mail Order POS without pre-authorization.

1. ***COMMITTEE ACTION: DRUGS DESIGNATED NF***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the products listed in Appendix D (listed by manufacturer) be designated nonformulary on the Uniform Formulary.

2. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) the following pre-authorization criteria for the drugs listed as nonformulary in Appendix D: 1) obtaining the product by home delivery would be detrimental to the patient; and, 2) for branded products with AB generic availability, use of the generic product would be detrimental to the patient. These pre-authorization criteria do not apply to any point of service other than retail network pharmacies.

3. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD FOR PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the drugs listed in Appendix D have 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the these decisions. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

4. ***COMMITTEE ACTION: DRUGS DESIGNATED FORMULARY***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the products listed in Appendix E (listed by manufacturer) be designated with the drug's previous status on the UF because the manufacturer has become compliant with refund requirements.

5. ***COMMITTEE ACTION: REMOVAL OF PRE-AUTHORIZATION CRITERIA*** The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that pre-authorization criteria for the drugs listed in Appendix E be removed because the manufacturer has become compliant with refund requirements.

6. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD FOR UF DESIGNATION AND REMOVAL OF PRE-AUTHORIZATION CRITERIA***—The P&T Committee

recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the formulary designation change and removal of pre-authorization criteria for drugs listed in Appendix E become effective upon signing of the minutes.

REMOVAL OF PRE-AUTHORIZATION CRITERIA
Effective upon my signature, when a manufacturer becomes compliant with FY2008 National Defense Authorization Act, Section 703, the previously imposed pre-authorization criteria are removed.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. SECTION 716 NDAA FY2013 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM

The P&T Committee was briefed on pending legislation requiring TRICARE for Life beneficiaries (≥ 65 years) to obtain refills for maintenance medications for chronic conditions through the TRICARE mail order pharmacy or at MTFs. Beneficiaries would be able to opt out after one year, and waivers would be granted on an individual basis, if deemed appropriate. Waivers would allow refills from the retail pharmacy in certain circumstances, including when necessary due to personal needs or hardship, emergency, or other special circumstances. The pilot program would run through December 31, 2017.

A. Medication Drug List for the Pilot Program

Candidate drugs for the Maintenance Medication Program must meet the following requirements: the medication is prescribed for a chronic, long-term condition; it is clinically appropriate to dispense the medication from the Mail Order Pharmacy; the medication is generally available at MTF pharmacies for initial prescription fill and refills; the medication is available for refill through the Mail Order Pharmacy; and, it is cost effective to dispense from the Mail Order Pharmacy.

1. ***COMMITTEE ACTION: MAINTENANCE MEDICATION PROGRAM DRUG LIST***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) the list of covered maintenance medications for the Section 716 pilot program. (See Appendix F.)

B. Manual PA Criteria for Waivers

Manual PA criteria (waivers) allowing for refills at the Retail Network for other

circumstances were discussed by the P&T Committee.

1. ***COMMITTEE ACTION: SECTION 716 MANUAL PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for maintenance medications for the following circumstances:
    a) Patient resides in a long-term care facility.
    b) Patient has other health insurance.
    c) Patient has barriers to receiving medications by mail (e.g., no permanent address, resides in rural setting).
    d) Patient is not on a stable dose of medication; the medication is currently being titrated.

Note: See Addendum from December 17, 2013, interim meeting.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, D.O., MPH
Lieutenant General, USAF, MC, CFS
Director

10 Feb 2014

Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

November 2013

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on November 13 and 14, 2013, at the Defense Health Agency (DHA) Pharmacoeconomic Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Lt. Gen. Douglas J. Robb D.O.., MPH, Director, DHA , approved the minutes for the August 2013 DoD P&T Committee meeting on November 7, 2013.
2. **Correction to the August 2013 Minutes**—The August minutes were corrected to state the implementation period for the self-monitoring blood glucose test strips will be 180 days, instead of 120 days. The implementation date is May 7, 2014.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors—Alogliptin (Nesina), Alogliptin/Metformin (Kazano), and Alogliptin/Pioglitazone (Oseni)

Relative Clinical Effectiveness Conclusion—Alogliptin (Nesina) is the fourth DPP-4 inhibitor to reach the market. Similar to the other DPP-4 inhibitors, it is combined with metformin (alogliptin/metformin; Kazano), but is the first DPP-4 inhibitor with a thiazolidinedione (TZD) combination [alogliptin/pioglitazone (Oseni)].

The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following with regard to the clinical efficacy and safety of the alogliptin-containing drugs:

- Alogliptin and the combinations with metformin and pioglitazone exhibit similar hemoglobin A1c (HbA1c) lowering effects compared to the other DPP-4 inhibitors. Dual therapy with alogliptin provided greater decreases in HbA1c from baseline in treatment naïve patients (HbA1c lowering of 1.22% to 1.71%) compared to patients previously treated with a DPP-4 inhibitor (HbA1c lowering of 0.39% to 0.6%). Triple therapy with alogliptin plus metformin and pioglitazone resulted in HbA1c changes from baseline ranging from 0.63% to 1.4%.
- Alogliptin, similar to the other DPP-4 inhibitors, is lipid- and weight-neutral and has minimal effects on blood pressure.
- The fixed-dose combinations of alogliptin with metformin or pioglitazone have the usual safety concerns (i.e., lactic acidosis, heart failure, fracture risk, edema, hepatic impairment, and bladder cancer).
- Alogliptin-containing products all require renal dosing.
- Although alogliptin is the only DPP-4 available in a fixed-dose combination with a TZD, it offers no additional clinical benefits, as alogliptin requires renal dosing and the multiple tablets strengths available may limit use.

Relative Cost-Effectiveness Conclusion—A cost minimization analysis (CMA) was performed. Based on the CMA results, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni) are more costly than the current UF (linagliptin products), BCF (sitagliptin products), and NF (saxagliptin products) DPP-4-inhibitors.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following:
    - alogliptin (Nesina), aloglptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni) be designated NF and non-preferred.
    - This recommendation includes step therapy, which requires a trial of a sitagliptin product (Januvia, Janumet, Janumet XR) (the preferred drugs) prior to using the other DPP4-inhibitors. Prior authorization for the DPP-4 inhibitors also requires a trial of metformin or sulfonylurea for new patients.
2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for alogliptin (Nesina),

alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
Existing automated PA (step therapy) requires a trial of metformin or a sulfonylurea prior to use of a DPP-4 inhibitor. Additionally, sitagliptin-containing products (Januvia, Janumet, Janumet XR) are the preferred agents in the DPP-4 inhibitors subclass. New users must try a preferred sitagliptin product before trying linagliptin or saxagliptin-containing products. Juvisync has been voluntarily discontinued from the market as of October 2013, and will no longer be a preferred sitagliptin product on the UF.

   The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) PA criteria should apply to alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni). (See Appendix C for the full criteria.)

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS); and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

B. Osteoporosis Drugs—Bisphosphonate Subclass: Alendronate Effervescent Tablet (Binosto)

Relative Clinical Effectiveness Conclusion—Effervescent alendronate (Binosto) is a new formulation of alendronate (Fosamax, generics). FDA approval was granted based on demonstrated bioequivalence to Fosamax 70 mg tablets. There are no clinical trials available with Binosto.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 2 absent):

- Effervescent alendronate (Binosto) may be more convenient for patients by requiring less consumption of water (4 ounces with Binosto versus 6–8 ounces with the other bisphosphonates) and to those patients with swallowing difficulties. It requires the same dosing and administration concerns as the other bisphosphonates.
- There is no data that Binosto is better tolerated or safer than other alendronate formulations. The high sodium content with Binosto is a disadvantage over other alendronate formulations.

- Binosto offers no clinically compelling advantages over current formulary bisphosphonate drugs.

Relative Cost-Effectiveness Conclusion—CMA was performed. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) effervescent alendronate (Binosto) is the least cost-effective oral bisphosphonate compared to current UF agents.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) effervescent alendronate (Binosto) be designated NF.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for effervescent alendronate (Binosto). (See Appendix B for the full criteria.)

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

V. UF DRUG CLASS REVIEWS

A. Short-Acting Beta Agonists (SABAs)

Relative Clinical Effectiveness Conclusion—The SABAs administered via metered dose inhalers (MDIs) were evaluated by the P&T Committee. The drugs in the class include albuterol [ProAir hydrofluoroalkane (HFA), Proventil HFA, Ventolin HFA] and levalbuterol (Xoponex HFA). The nebulized products were not evaluated. No new clinical conclusions were made since the SABAs Drug Class was reviewed in November 2011. The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 1 absent) with the following conclusions:

- There are no studies in either adults or children assessing efficacy of albuterol versus levalbuterol when administered via MDIs for treating asthma.
- In exercise-induced bronchospasm (EIB), albuterol administered via MDI taken 15–30 minutes before exercise prevents symptoms significantly better than placebo. Although Xopenex HFA is not currently approved by the FDA for EIB, phase III trials point to similar effect size as with albuterol.
- For chronic obstructive pulmonary disease, the SABAs are more efficacious than placebo. There is insufficient evidence to compare the efficacy of albuterol versus levalbuterol.

- Although there is a lack of comparative safety data between levalbuterol and albuterol MDIs, there is no evidence to suggest clinically relevant differences in safety between the drugs.
- Since the last UF review, ProAir HFA now includes a dose counter. Ventolin HFA also has a dose counter. Proventil HFA and Xopenex HFA do not have dose counters.
- Although the FDA states albuterol HFA products are separate entities and not substitutable, clinically there is a high degree of therapeutic interchangeability between ProAir HFA, Proventil HFA, Ventolin HFA, and Xoponex HFA.
- To meet the needs of Military Health System (MHS) patients, only one SABA is needed on the BCF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 3 absent) that among SABA HFA metered dose inhalers, ProAir HFA was the most cost-effective agent based on the weighted average cost per day of treatment across all three POS, followed by Xopenex HFA, Ventolin HFA, and Proventil HFA. Results from the CMA and budget impact analysis (BIA) showed that designating ProAir HFA as the sole UF agent in this class, with all other SABA HFA MDIs designated as NF, was the most cost-effective scenario for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) that ProAir HFA remain designated formulary on the UF. The P&T Committee also recommended that Proventil HFA, Ventolin HFA, and Xopenex HFA be designated NF on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***— The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) that ProAir HFA should be added to the BCF and Ventolin HFA should be removed from the BCF. The P&T Committee also recommended that local Military Treatment Facility (MTF) P&T Committees rapidly convert patients to ProAir HFA and provide patient education on proper inhaler technique.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) MN criteria for Proventil HFA, Ventolin HFA, and Xopenex HFA. (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 3 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is May 14, 2014.

B. Benign Prostatic Hyperplasia Agents—5-Alpha Reductase Inhibitors (5-ARIs) Subclass

Relative Clinical Effectiveness Analysis and Conclusion—The 5-ARIs include finasteride (Proscar, generics), dutasteride (Avodart), and the combination product dutasteride/tamsulosin (Jalyn), which contains an alpha-1 blocker (A1B). The 5-ARIs were previously reviewed for UF placement in May 2007. Jalyn was previously reviewed as a new drug in the A1B subclass in May 2011. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following for the 5-ARIs:

- The 5-ARIs finasteride and dutasteride (Avodart) improve lower urinary tract symptoms associated with benign prostatic hypertrophy (BPH), when compared to placebo. Because of the placebo effect in reducing symptoms, the magnitude of the effect due to treatment is small and may not be clinically significant.
- Finasteride and dutasteride (Avodart) appear interchangeable with regard to efficacy in treating lower urinary tract symptoms associated with BPH. Both agents result in similar decreases in prostate volume, increases in urinary flow rate, and improvement in symptoms. Similar reductions in risk of acute urinary retention and BPH-related surgery are seen with both agents.
- The 5-ARIs are most useful in men who have enlarged prostates, but show little efficacy in men with normal prostate volumes.
- Finasteride and dutasteride (Avodart) exhibit a high degree of therapeutic interchangeability. Either finasteride or dutasteride is expected to meet the needs of the majority of benign prostatic hyperplasia patients in the MHS. Neither drug offers a unique benefit. It is unlikely that a patient who did not have an adequate response with one 5-ARI would have an improved response with the other.
- The combination product dutasteride/tamsulosin (Jalyn) confers no additional benefit when compared with using the individual components together. As the 5-ARIs are highly interchangeable, it likely makes little clinical difference which 5-ARI is used in combination with an A1B.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed to evaluate the 5-ARI subclass. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that finasteride was the most cost-effective agent in this class. Dutasteride (Avodart) and dutasteride/ tamsulosin (Jalyn) were not cost-effective when compared with finasteride alone or in combination with generic uroselective A1Bs (tamsulosin or alfuzosin).
- BIA was performed to evaluate the potential impact of scenarios with selected 5ARIs designated formulary or nonformulary on the UF. BIA results showed the scenario with finasteride designated as formulary on the UF, and dutasteride (Avodart) and

dutasteride/tamsulosin (Jalyn) designated as nonformulary on the UF was the most cost-effective for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following:

    - finasteride (Proscar, generic) remain designated with formulary status on the UF; and
    - dutasteride (Avodart) and dutasteride/tamsulosin (Jalyn) be designated NF.
    - This recommendation includes step therapy, which requires a trial of a finasteride prior to using dutasteride (Avodart) in all current and new patients, or dutasteride/tamsulosin (Jalyn) in new users.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T recommended (15 for, 0 opposed, 1 abstained, 0 absent) that finasteride remain as the designated 5-ARI product on the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) MN criteria for dutasteride (Avodart) and dutasteride/tamsulosin (Jalyn). (See Appendix B for the full criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) PA criteria should apply to the nonformulary 5-ARIs. A trial of finasteride is required prior to using dutasteride (Avodart) in all current and new patients, or dutasteride/tamsulosin (Jalyn) in all new users. With the new requirement for use of finasteride prior to using Jalyn, the previous prior authorization criteria where a trial of alfuzosin or tamsulosin was required no longer apply. (See Appendix C for full PA criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, abstained, 4 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

VI. UTILIZATION MANAGEMENT

A. PAs

1. **Multiple Sclerosis (MS) Drugs: Dimethyl Fumarate (Tecfidera)**—Dimethyl fumarate is an oral disease modifying drug for MS that was FDA-approved in March 2013. The drug has not yet been reviewed for UF status. The package insert recommends measuring the complete blood count (CBC) within six months prior to initiation of therapy, due to the risk of lymphopenia. PA criteria apply to the other MS drugs.

    a) ***COMMITTEE ACTION: DIMETHYL FUMARATE (TECFIDERA) PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for dimethyl fumarate (Tecfidera) for relapsing forms of MS, and CBC monitoring, consistent with the product labeling. (See Appendix C for full criteria.)

2. **Targeted Immunomodulatory Biologics (TIBs): Certolizumab (Cimzia), Tocilizumab (Actemra), and Ustekinumab (Stelara)**—PA criteria currently apply to the TIBs. Tocilizumab was previously limited to injection by health care professionals, but is now available in pre-filled syringes labeled for patient self administration for treatment of rheumatoid arthritis. The FDA recently approved new indications for certolizumab for treatment of ankylosing spondylitis (AS) and psoriatic arthritis (PsA), and ustekinumab for treatment of PsA.

    a) ***COMMITTEE ACTION: CERTOLIZUMAB (CIMZIA), TOCILIZUMAB (ACTEMRA), AND USTEKINUMAB (STELARA) PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for certolizumab for AS and PsA, tocilizumab for rheumatoid arthritis, and ustekinumab for PsA, consistent with the products' labeling. (See Appendix C for full criteria.)

B. Quantity Limits (QLs)

1. **TIB: Tocilizumab (Actemra)**—QLs currently apply to the TIBs. The P&T Committee evaluated QLs for tocilizumab for treatment of rheumatoid arthritis.

    a) ***COMMITTEE ACTION: TOCILIZUMAB (ACTEMRA) QLs***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) QLs for Actemra (162 mg/0.9 mL), limiting use to 4 pre-filled syringes per 28 days in the Retail Network, and 8 pre-filled syringes per 56 days via Mail Order, consistent with FDA-approved product labeling.

C. Copayment Change

1. **Niacin ER (Niaspan)**—The P&T Committee reviewed pricing for niacin ER (Niaspan). AB-rated generics are available for this product, but the branded product has significantly lower pricing.

    a) ***COMMITTEE ACTION: COPAYMENT CHANGE***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the Tier 1 copayment be assigned for Niaspan.

    b) ***COMMITTEE ACTION: COPAYMENT IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the Tier 1 copayment change for Niaspan become effective upon signing of the minutes.

VII. FY2008 NATIONAL DEFENSE AUTHORIZATION ACT (NDAA), SECTION 703

A. Section 703—The P&T Committee reviewed drugs from manufacturers that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not compliant with FY2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the Retail POS and medical necessity in MTFs. These NF drugs will remain available in the Mail Order POS without pre-authorization.

1. ***COMMITTEE ACTION: DRUGS DESIGNATED NF***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the products listed in Appendix D (listed by manufacturer) be designated nonformulary on the Uniform Formulary.

2. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) the following pre-authorization criteria for the drugs listed as nonformulary in Appendix D: 1) obtaining the product by home delivery would be detrimental to the patient; and, 2) for branded products with AB generic availability, use of the generic product would be detrimental to the patient. These pre-authorization criteria do not apply to any point of service other than retail network pharmacies.

3. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD FOR PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the drugs listed in Appendix D have 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2)

DHA send a letter to beneficiaries affected by these decisions. Based on the P&T Committee's recommendation, the effective date is April 16, 2014.

4. ***COMMITTEE ACTION: DRUGS DESIGNATED FORMULARY***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the products listed in Appendix E (listed by manufacturer) be designated with the drug's previous status on the UF because the manufacturer has become compliant with refund requirements.

5. ***COMMITTEE ACTION: REMOVAL OF PRE-AUTHORIZATION CRITERIA*** The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that pre-authorization criteria for the drugs listed in Appendix E be removed because the manufacturer has become compliant with refund requirements.

6. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD FOR UF DESIGNATION AND REMOVAL OF PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) that the formulary designation change and removal of pre-authorization criteria for drugs in Appendix E become effective upon signing of the minutes.

   REMOVAL OF PRE-AUTHORIZATION CRITERIA
   Effective upon signature of the Director, DHA, when a manufacturer becomes compliant with FY2008 National Defense Authorization Act, Section 703, the previously imposed pre-authorization criteria are removed.

VIII. SECTION 716 NDAA FY2013 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM

The P&T Committee was briefed on pending legislation requiring TRICARE for Life beneficiaries ($\geq$ 65 years) to obtain refills for maintenance medications for chronic conditions through the TRICARE mail order pharmacy or at MTFs. Beneficiaries would be able to opt out after one year, and waivers would be granted on an individual basis, if deemed appropriate. Waivers would allow refills from the retail pharmacy in certain circumstances, including when necessary due to personal needs or hardship, emergency, or other special circumstances. The pilot program would run through December 31, 2017.

A. Medication Drug List for the Pilot Program

Candidate drugs for the Maintenance Medication Program must meet the following requirements: the medication is prescribed for a chronic, long-term condition; it is clinically appropriate to dispense the medication from the Mail Order Pharmacy; the medication is generally available at MTF pharmacies for initial prescription fill and refills; the medication is

available for refill through the Mail Order Pharmacy; and, it is cost effective to dispense from the Mail Order Pharmacy.

1. ***COMMITTEE ACTION: MAINTENANCE MEDICATION PROGRAM DRUG LIST***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) the list of covered maintenance medications for the Section 716 pilot program. (See Appendix F.)

B. Manual PA Criteria for Waivers

Manual PA criteria (waivers) allowing for refills at the Retail Network for other circumstances were discussed by the P&T Committee.

1. ***COMMITTEE ACTION: SECTION 716 MANUAL PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 3 absent) PA criteria for maintenance medications for the following circumstances:
   a) Patient resides in a long-term care facility.
   b) Patient has other health insurance.
   c) Patient has barriers to receiving medications by mail (e.g., no permanent address, resides in rural setting).
   d) Patient is not on a stable dose of medication; the medication is currently being titrated.

Note: See Addendum from December 17, 2013, interim meeting.

IX. ITEMS FOR INFORMATION

A. Zolpidem and Gender Dosing—The FDA recommended new dosing guidelines for zolpidem and zolpidem extended release (ER) in January 2013, limiting dosing in females to 5 mg and 6.25 mg, respectively. The new dosing recommendations are based on data showing blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. In February 2013, the P&T Committee recommended monitoring zolpidem prescribing practices in the MHS. A review of zolpidem prescribing in women in the MHS shows that utilization of the lower doses of zolpidem and zolpidem ER in women has increased since January 2013, particularly at the MTFs. The P&T Committee recommended continued monitoring.

B. Acthar Gel PA Implementation Date—PA criteria and a 30-day PA implementation period for Acthar Gel were recommended at the August 2013 Committee meeting. The implementation date will be December 18, 2013.

C. **Points of Service Analysis Update**— The Pharmacy Outcomes Research Team (PORT) updated the P&T Committee on comparative drug costs across all three POS. Data from the third quarter in Fiscal Year (FY) 2013 showed drug costs for branded non-specialty maintenance medications (i.e., medications used for chronic conditions and not specialty medications) would have been lower overall if all prescriptions dispensed in the retail network during that quarter had instead been dispensed at MTFs or in mail order. Higher drug costs for brand medications at retail were primarily responsible for the cost differences. Costs for generically available non-specialty medications would have slightly increased. Fourth quarter results from FY12 are comparable; however, improved availability of generics for widely-used medications at MTFs (e.g., clopidogrel, atorvastatin) and in mail order have generated greater cost avoidance for the MHS in FY2013.

D. **Drug Utilization & Costs**—The PORT reported preliminary results of specialty drug utilization and costs across the MHS. This analysis used a broad list of specialty medications and was adjusted for retail refunds. Specialty medications accounted for about 19% of expenditures in FY2013, but fewer than 1% of total 30-day equivalent prescriptions. Prescriptions dispensed from the retail network accounted for about 66% of specialty medication spend, followed by MTFs (18%), and mail order (16%). Top specialty classes by total cost included oral oncologic agents, TIBs, and MS agents. The PORT also reported total FY2013 expenditures for the top 25 drugs and drug classes by cost, across both specialty and non-specialty agents.

E. **Specialty Care Medications**—The P&T Committee was briefed on potential options for utilization management for specialty medications. The list of specialty medications for inclusion in specialty care programs is in the process of being updated, and will be presented at a future meeting.

F. **Bulk Chemicals in Compounded Medications**—The P&T Committee was presented with an update on the status of bulk chemicals in compounded medications. Future updates will be provided when a final recommendation is available.

X. ADJOURNMENT

The meeting adjourned at 1145 hours on November 14, 2013. The next meeting will be in February 2014.

Appendix A—Attendance: November 2013 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Drugs Designated Nonformulary due to Section 703

Appendix E—Table of Drugs Returned to Uniform Formulary due to Section 703

Appendix F—Section 716 Maintenance Medication Program Drug List

Appendix A—Attendance: November 2013 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
LTC Robert Conrad, MS	Chief, DHA Pharmacoeconomic Branch (Recorder)
CDR Joseph Lawrence, MSC for Col George Jones, BSC	Deputy Chief, DHA Pharmacy Operations Division
COL John Spain, MS	Army, Pharmacy Officer
Col Scott Sprenger, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Michael Wynn, MC	Army, Family Practice Physician
LCDR Carey Welsh, MC	Navy, Pediatrics Rep
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
LTC Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Maj Temple Ratcliff, MC for Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. Paul Hutter for Mr. David Hurt	Associate General Counsel, DHA
Capt Richard Caballero, via DCO	Defense Logistics Agency Troop Support
Guests	
Mr. Bill Davies via DCO	Defense Health Agency, Pharmacy Operations Division
CDR Matthew Baker via DCO	Indian Health Service

Appendix A—Attendance (continued)

Others Present	
CAPT Walter Downs, MC	DHA Pharmacoeconomic Branch
LCDR Marisol Martinez, USPHS	DHA Pharmacoeconomic Branch
LCDR Joshua Devine, USPHS	DHA Pharmacoeconomic Branch
LCDR Linh Quach, MSC	DHA Pharmacoeconomic Branch
Maj David Folmar, BSC	DHA Pharmacoeconomic Branch
MAJ Misty Cowan, MC	DHA Pharmacoeconomic Branch
Dr. David Meade	DHA Pharmacoeconomic Branch
Dr. Angela Allerman	DHA Pharmacoeconomic Branch
Dr. Shana Trice	DHA Pharmacoeconomic Branch
Dr. Dean Valibhai	DHA Pharmacoeconomic Branch
Dr. Jeremy Briggs	DHA Pharmacoeconomic Branch
Dr. Brian Beck	DHA Pharmacoeconomic Branch
Dr. Amy Lugo	DHA Pharmacoeconomic Branch
LT Kendra Jenkins, USPHS, via DCO	DHA Pharmacy Operations Division
Ms. Deborah Garcia	DHA Pharmacoeconomic Branch contractor
Dr. Esmond Nwokeji	DoD Pharmacoeconomic Branch contractor
Mr. Kirk Stocker	DoD Pharmacoeconomic Branch contractor
Maj Ellen Roska, BSC	University of Texas PhD student
Andrew Delgado	University of Texas Health Science Center/University of Texas College of Pharmacy student
Roderick Sanchez	University of Incarnate Word, Feik School of Pharmacy student
Ankita Patel	University of Incarnate Word, Feik School of Pharmacy student
James Flink	University of Incarnate Word, Feik School of Pharmacy student

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Alogliptin (Nesina) • Alogliptin/metformin (Kazano) • Alogliptin/pioglitazone (Oseni) **Dipeptidyl-Peptidase-4 (DPP-4) Inhibitors**	• Use of sitagliptin- or linagliptin-containing products is contraindicated. • The patient has experienced significant adverse effects from sitagliptin- or linagliptin-containing products. • There is no alternative formulary agent: the patient requires a thiazolidinedione but cannot take the 2 drugs separately.
• Effervescent alendronate (Binosto) **Osteoporosis Drugs – Bisphosphonates**	• There is no alternative formulary agent: the patient cannot swallow tablets or cannot consume 8oz. of water and has no sodium restrictions.
• Proventil HFA • Ventolin HFA • Xoponex HFA **Short-Acting Beta Agonist Metered Dose Inhalers**	• The patient previously responded to a nonformulary agent and changing to a formulary agent would incur unacceptable risk.
• Dutasteride (Avodart) **BPH Drugs – 5-Alpha Reductase Inhibitors (5-ARI)**	• Use of finasteride is contraindicated (e.g., hypersensitivity). • The patient has experienced significant adverse effects from finasteride.
• Dutasteride/tamsulosin (Jalyn) **BPH Drugs – 5-Alpha Reductase Inhibitors (5-ARI)**	• Use of finasteride is contraindicated (e.g., hypersensitivity) and the patient requires therapy with both an alpha-1 receptor blocker (A1B) and 5-ARI. • The patient has experienced significant adverse effects from finasteride, and requires therapy with both an A1B and 5-ARI. • There is no alternative formulary agent: the patient is unable to take finasteride (due to contraindication or adverse effect), requires therapy with both an A1B and a 5-ARI, and requires a fixed-dose combination due to, for example, swallowing difficulties.

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Alogliptin (Nesina) • Alogliptin/metformin (Kazano) • Alogliptin/pioglitazone (Oseni) **Dipeptidyl-Peptidase-4 (DPP-4) Inhibitors**	All new and current users of a DPP-4 inhibitor are required to try metformin or a sulfonylurea before receiving a DPP-4 inhibitor. Additionally, sitagliptin-containing products (Januvia, Janumet, Janumet XR) are the preferred agents in the DPP-4 inhibitors subclass. New users of alogliptin must try a sitagliptin product first. Automated PA criteria • The patient has filled a prescription for metformin or a sulfonylurea at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. • The patient has received a prescription for a preferred DPP-4 inhibitor (Januvia, Janumet, or Janumet XR) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—If automated criteria are not met, alogliptin, alogliptin/metformin, or alogliptin/pioglitazone is approved (e.g., trial of metformin or a sulfonylurea is NOT required) if: • The patient has had an inadequate response to metformin or sulfonylurea. • The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis [for alogliptin (Nesina) or alogliptin/pioglitazone (Oseni)]. • The patient has experienced the following adverse event while receiving a sulfonylurea: hypoglycemia requiring medical treatment. • The patient has a contraindication to metformin or a sulfonylurea. AND In addition to the above criteria regarding metformin and sulfonylurea, the following PA criteria would apply specifically to alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni): • The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with alogliptin-containing products. • The patient has had an inadequate response to a sitagliptin-containing product. • The patient has a contraindication to sitagliptin.

Drug / Drug Class	Prior Authorization Criteria
• Dutasteride (Avodart) **BPH Drugs – 5-Alpha Reductase Inhibitors (5-ARIs)**	All new and current users of Avodart are required to try finasteride. Automated PA criteria • The patient has filled a prescription for finasteride at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—If automated criteria are not met, Avodart is approved (e.g., trial of finasteride is NOT required) if: • Use of generic finasteride is contraindicated (e.g., due to hypersensitivity). • Patient has experienced or is likely to experience significant adverse effects from finasteride.
• Dutasteride/tamsulosin (Jalyn) **BPH Drugs – 5-Alpha Reductase Inhibitors (5-ARIs)**	All new users of Jalyn are required to try finasteride. With the new requirement for use of finasteride prior to using Jalyn, the previous prior authorization criteria where a trial of alfuzosin or tamsulosin was required no longer apply. Automated PA criteria • The patient has a previous step therapy (automated prior authorization) approval for dutasteride/tamsulosin (Jalyn), or • The patient has filled a prescription for finasteride at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—If automated criteria are not met, Jalyn is approved (e.g., trial of finasteride is NOT required) if: • Use of finasteride is contraindicated and the patient requires therapy with both an alpha-1 receptor blocker (A1B) and a 5-ARI. • The patient has tried finasteride, was unable to tolerate it due to adverse effects, and requires therapy with both an A1B and a 5-ARI. • The patient is unable to take finasteride (due to a contraindication or adverse events), requires therapy with both an A1B and a 5-ARI, and requires a fixed-dose combination due to, for example, swallowing difficulties.

Drug / Drug Class	Prior Authorization Criteria
• Dimethyl fumarate (Tecfidera) **Multiple Sclerosis**	Coverage approved for patients with: • Documented diagnosis of relapsing forms of multiple sclerosis (MS). • Complete blood count drawn within six months prior to imitation of therapy, due to risk of lymphopenia. • Coverage NOT provided for concomitant use with other disease-modifying drugs of MS.
• Certolizumab (Cimzia) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: • **Active ankylosing spondylitis** • **Active psoriatic arthritis** • Moderately to severely active Crohn's disease refractory to conventional therapy • Moderately to severely active rheumatoid arthritis • Coverage NOT provided for concomitant use with other TIBs, Kineret, Enbrel, Remicade, Orencia, or Rituxan
• Tocilizumab (Actemra) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: • Moderate to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying antirheumatic drugs • Not approved for use in systemic or polyarticular juvenile idiopathic arthritis
• Ustekinumab (Stelara) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: • **Active psoriatic arthritis** • Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy • Coverage NOT provided for concomitant use with other TIBs, Kineret, Enbrel, Remicade, Orencia, or Rituxan

Appendix D—Table of Drugs Designated Nonformulary due to Section 703

The drugs below are designated NF on the UF and pre-authorization is assigned.

Manufacturer	Drugs
LUPIN PHAR	ANTARA
MISSION PH	BINOSTO LITHOSTAT THIOLA TINDAMAX UROCIT-K (10 MEQ) UROCIT-K (15 MEQ) UROCIT-K (5 MEQ)
ROMARK LAB	ALINIA
WESTWARD	ATIVAN ATIVAN INJECTION DOPRAM DURAMORPH GLYCOPYRROLATE INFUMORPH ROBAXIN ROBINUL

Appendix E—Table of Drugs Returned to Uniform Formulary due to Section 703

The drugs below, except where noted, are returned to formulary status on the UF and pre-authorization is removed.

Manufacturer	Drugs
ALLERGAN	ALOCRIL AVAGE AZELEX BETAGAN BLEPHAMIDE ELESTAT ELIMITE FML FML FORTE FML S.O.P. OCUFEN OCUFLOX POLY-PRED POLYTRIM PRED MILD PRED-G
BAXTER	TRANSDERM-SCOP
BEDFORD LABS	CAFCIT GLUCAGEN
BIOVITRUM	KINERET
DAVA	RHEUMATREX (REMAINS NF, NO PRE-AUTHORIZATION)
FRESENIUS MED	PHOSLO

Appendix F—Section 716 Maintenance Medication Program Drug List

5-ALPHA-REDUCTASE INHIBITORS
JALYN
PROSCAR
ADRENALS
CORTEF
ALKALINIZING AGENTS
UROCIT-K
ALPHA-ADRENERGIC AGONISTS (EENT)
ALPHAGAN P
COMBIGAN
ALPHA-ADRENERGIC BLOCKING AGENT(SYMPATH)
FLOMAX
UROXATRAL
ALPHA-ADRENERGIC BLOCKING AGENTS
CARDURA
MINIPRESS
ALPHA-GLUCOSIDASE INHIBITORS
GLYSET
PRECOSE
AMINOGLYCOSIDES
TOBI
AMMONIA DETOXICANTS
KRISTALOSE
AMYLINOMIMETICS
SYMLIN
SYMLINPEN 120
SYMLINPEN 60
ANGIOTENSIN II RECEPTOR ANTAGONISTS
ATACAND
ATACAND HCT
AVALIDE
AVAPRO
BENICAR
BENICAR HCT
COZAAR
DIOVAN
DIOVAN HCT
EDARBI
EDARBYCLOR
DOPAMINE RECEPTOR AGONISTS
MIRAPEX
MIRAPEX ER
NEUPRO
REQUIP
REQUIP XL
EENT ANTI-INFLAMMATORY AGENTS, MISC.
RESTASIS
EENT DRUGS, MISCELLANEOUS
IOPIDINE
ESTROGEN AGONIST-ANTAGONISTS
EVISTA
ESTROGENS
ACTIVELLA
ALORA
ANGELIQ
CENESTIN
CLIMARA
CLIMARA PRO
COMBIPATCH
DIVIGEL
ELESTRIN
ENJUVIA
ESTRACE
ESTRADERM
ESTRASORB
ESTRING
ESTROGEL
FEMHRT
FEMRING
FEMTRACE
MENEST
MENOSTAR
MINIVELLE
PREFEST
PREMARIN
PREMPHASE
PREMPRO
VAGIFEM

ANGIOTENSIN II RECEPTOR ANTAGONISTS
HYZAAR
MICARDIS
MICARDIS HCT
TEVETEN
TEVETEN HCT
TWYNSTA
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS
ACCUPRIL
ACCURETIC
ACEON
ALTACE
LOTENSIN
LOTENSIN HCT
MAVIK
PRINIVIL
TARKA
UNIRETIC
UNIVASC
VASERETIC
VASOTEC
ZESTORETIC
ZESTRIL
ANTIARRHYTHMIC AGENTS
CORDARONE
MULTAQ
NORPACE
NORPACE CR
RYTHMOL
RYTHMOL SR
TAMBOCOR
ANTICOAGULANTS
ARIXTRA
FRAGMIN
LOVENOX
PRADAXA
ANTIDEPRESSANTS
CELEXA
EFFEXOR XR
LEXAPRO
LUVOX CR
MARPLAN

ESTROGENS
VIVELLE-DOT
FIBRIC ACID DERIVATIVES
ANTARA
FENOGLIDE
FIBRICOR
LIPOFEN
LOFIBRA
LOPID
TRICOR
TRIGLIDE
TRILIPIX
HEMATOPOIETIC AGENTS
ARANESP
EPOGEN
LEUKINE
NEULASTA
NEUMEGA
NEUPOGEN
PROCRIT
HEMORRHEOLOGIC AGENTS
TRENTAL
HISTAMINE H2-ANTAGONISTS
AXID
PEPCID
ZANTAC
ZANTAC 25
HMG-COA REDUCTASE INHIBITORS
ADVICOR
ALTOPREV
CADUET
CRESTOR
LESCOL
LESCOL XL
LIPITOR
MEVACOR
PRAVACHOL
SIMCOR
ZOCOR
IMMUNOMODULATORY AGENTS
AVONEX
AVONEX ADMINISTRATION PACK

ANTIDEPRESSANTS
NARDIL
PARNATE
PAXIL
PEXEVA
PROZAC
VENLAFAXINE HCL ER
WELLBUTRIN
WELLBUTRIN SR
WELLBUTRIN XL
ZOLOFT
ANTIGOUT AGENTS
ULORIC
ZYLOPRIM
ANTI-INFLAMMATORY AGENTS (GI DRUGS)
APRISO
ASACOL HD
CANASA
DIPENTUM
LIALDA
LOTRONEX
PENTASA
DELZICOL
ANTILIPEMIC AGENTS, MISCELLANEOUS
LOVAZA
NIASPAN
ANTIMUSCARINICS
DETROL
DETROL LA
DITROPAN XL
SANCTURA
SANCTURA XR
VESICARE
ANTIMUSCARINICS/ANTISPASMODICS
ATROVENT HFA
CUVPOSA
SPIRIVA
ANTIMYCOBACTERIALS, MISCELLANEOUS
DAPSONE
ANTIRETROVIRALS
FUZEON
ANTITHYROID AGENTS
TAPAZOLE

IMMUNOMODULATORY AGENTS
AVONEX PEN
BETASERON
COPAXONE
REBIF
INCRETIN MIMETICS
BYDUREON
BYETTA
VICTOZA 2-PAK
VICTOZA 3-PAK
INSULINS
APIDRA
APIDRA SOLOSTAR
HUMALOG
HUMALOG MIX 50-50
HUMALOG MIX 75-25
HUMULIN 70-30
HUMULIN N
LANTUS
LANTUS SOLOSTAR
LEVEMIR
NOVOLIN 70-30
NOVOLIN N
NOVOLOG
NOVOLOG FLEXPEN
NOVOLOG MIX 70-30
NOVOLOG MIX 70-30 FLEXPEN
INTERFERONS
INTRON A
PEGASYS
PEGINTRON
PEGINTRON REDIPEN
LEUKOTRIENE MODIFIERS
ACCOLATE
SINGULAIR
LOOP DIURETICS
DEMADEX
EDECRIN
LASIX
MEGLITINIDES
PRANDIMET
PRANDIN
STARLIX

BETA-ADRENERGIC AGONISTS
- ARCAPTA NEOHALER
- BROVANA
- SEREVENT DISKUS
- VOSPIRE ER

BETA-ADRENERGIC BLOCKING AGENTS
- BETAPACE
- BETAPACE AF
- COREG
- COREG CR
- CORGARD
- CORZIDE
- DUTOPROL
- INDERAL LA
- INNOPRAN XL
- KERLONE
- LEVATOL
- LOPRESSOR
- LOPRESSOR HCT
- SECTRAL
- TENORETIC 100
- TENORETIC 50
- TENORMIN
- TOPROL XL
- TRANDATE
- ZEBETA
- ZIAC

BETA-ADRENERGIC BLOCKING AGENTS (EENT)
- BETAGAN
- BETOPTIC S
- OPTIPRANOLOL
- TIMOPTIC
- TIMOPTIC OCUDOSE
- TIMOPTIC-XE

BIGUANIDES
- GLUCOPHAGE
- GLUCOPHAGE XR
- RIOMET

BILE ACID SEQUESTRANTS
- COLESTID
- QUESTRAN

MINERALOCORTICOID (ALDOSTERONE) ANTAGNTS
- ALDACTAZIDE
- ALDACTONE
- INSPRA

MIOTICS
- ISOPTO CARBACHOL
- ISOPTO CARPINE
- PHOSPHOLINE IODIDE
- PILOPINE HS

MONOAMINE OXIDASE B INHIBITORS
- AZILECT
- ELDEPRYL
- ZELAPAR

MUCOLYTIC AGENTS
- PULMOZYME

MYDRIATICS
- CYCLOGYL
- CYCLOMYDRIL
- ISOPTO ATROPINE
- ISOPTO HOMATROPINE
- ISOPTO HYOSCINE
- MYDRIACYL

NITRATES AND NITRITES
- DILATRATE-SR
- IMDUR
- ISOCHRON
- ISORDIL
- ISORDIL TITRADOSE
- MINITRAN
- MONOKET
- NITRO-DUR

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS
- ANAPROX
- ANAPROX DS
- ARTHROTEC 50
- ARTHROTEC 75
- BUTALBITAL-ASPIRIN-CAFFEINE
- CELEBREX
- CLINORIL
- DAYPRO
- EC-NAPROSYN

BILE ACID SEQUESTRANTS
- QUESTRAN LIGHT

BONE RESORPTION INHIBITORS
- ACTONEL
- BONIVA
- DIDRONEL
- FOSAMAX
- FOSAMAX PLUS D
- SKELID

CALCIUM-CHANNEL BLOCKING AGENTS, MISC.
- CALAN
- CALAN SR
- CARDIZEM
- CARDIZEM CD
- DILACOR XR
- ISOPTIN SR
- TIAZAC

CARBONIC ANHYDRASE INHIBITORS (EENT)
- COSOPT
- COSOPT PF
- DIAMOX SEQUELS
- NEPTAZANE
- TRUSOPT

CARDIAC DRUGS, MISCELLANEOUS
- RANEXA

CARDIOTONIC AGENTS
- LANOXIN

CATECHOL-O-METHYLTRANSFERASE (COMT) INHIBITORS
- COMTAN
- TASMAR

CENTRAL ALPHA-AGONISTS
- CATAPRES
- CATAPRES-TTS 1
- CATAPRES-TTS 2
- CATAPRES-TTS 3
- CLORPRES
- NEXICLON XR
- TENEX

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS
- FELDENE
- MOBIC
- NALFON
- NAPROSYN
- VIMOVO
- VOLTAREN
- VOLTAREN-XR

NUCLEOSIDES AND NUCLEOTIDES
- COPEGUS
- REBETOL

OTHER MISCELLANEOUS THERAPEUTIC AGENTS
- CARNITOR
- POTABA

PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS)
- ARICEPT
- ARICEPT ODT
- EVOXAC
- EXELON
- MESTINON
- RAZADYNE
- RAZADYNE ER

PARATHYROID
- FORTEO

PITUITARY
- DDAVP
- NORDITROPIN FLEXPRO
- NORDITROPIN NORDIFLEX
- NUTROPIN
- NUTROPIN AQ
- NUTROPIN AQ NUSPIN
- SAIZEN
- STIMATE
- TEV-TROPIN

PLATELET-AGGREGATION INHIBITORS
- BRILINTA
- EFFIENT
- PLAVIX
- PLETAL

CENTRAL NERVOUS SYSTEM AGENTS, MISC.
LODOSYN
ZANAFLEX
CHOLELITHOLYTIC AGENTS
ACTIGALL
URSO
URSO FORTE
CHOLESTEROL ABSORPTION INHIBITORS
VYTORIN
ZETIA
CORTICOSTEROIDS (RESPIRATORY TRACT)
ADVAIR DISKUS
ADVAIR HFA
ASMANEX
DULERA
FLOVENT DISKUS
FLOVENT HFA
PULMICORT
SYMBICORT
DIHYDROPYRIDINES
ADALAT CC
AZOR
EXFORGE
EXFORGE HCT
LOTREL
NORVASC
PROCARDIA
PROCARDIA XL
DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS
JANUMET
JANUMET XR
JANUVIA
JENTADUETO
DIRECT VASODILATORS
BIDIL
PROGLYCEM
DIRECT-ACTING SKELETAL MUSCLE RELAXANTS
DANTRIUM
POTASSIUM-SPARING DIURETICS
DYAZIDE
DYRENIUM
MAXZIDE
MAXZIDE-25 MG
MIDAMOR
PROGESTINS
AYGESTIN
PROMETRIUM
PROVERA
PROSTAGLANDIN ANALOGS
LUMIGAN
XALATAN
PROSTAGLANDINS
CYTOTEC
PROTECTANTS
CARAFATE
PROTON-PUMP INHIBITORS
NEXIUM
PRILOSEC
PRILOSEC OTC
PROTONIX
ZEGERID OTC
RENIN INHIBITORS
AMTURNIDE
TEKTURNA
TEKTURNA HCT
VALTURNA
REPLACEMENT PREPARATIONS
EFFER-K
KLOR-CON
K-TAB
MICRO-K
RESPIRATORY SMOOTH MUSCLE RELAXANTS
DILEX-G 200
DILEX-G 400
ELIXOPHYLLIN
LUFYLLIN
LUFYLLIN-GG
THEO-24

DOPAMINE PRECURSORS PARCOPA SINEMET 10-100 SINEMET 25-100 SINEMET 25-250 SINEMET CR STALEVO 100 STALEVO 125 STALEVO 150 STALEVO 200 STALEVO 50 STALEVO 75	**SOMATOSTATIN AGONISTS** SANDOSTATIN SANDOSTATIN LAR **SULFONAMIDES (SYSTEMIC)** AZULFIDINE **SULFONYLUREAS** AMARYL DIABETA GLUCOTROL GLUCOTROL XL GLUCOVANCE GLYNASE METAGLIP
VITAMIN D HECTOROL ROCALTROL ZEMPLAR **VASODILATING AGENTS, MISCELLANEOUS** AGGRENOX PERSANTINE **VITAMIN B COMPLEX** NASCOBAL **PHOSPHODIESTERASE-5 INHIBITORS** VIAGRA	**THIAZIDE DIURETICS** DIURIL MICROZIDE **THIAZIDE-LIKE DIURETICS** THALITONE ZAROXOLYN **THIAZOLIDINEDIONES** ACTOPLUS MET ACTOPLUS MET XR ACTOS DUETACT
PLATELET-REDUCING AGENTS AGRYLIN	**THYROID AGENTS** ARMOUR THYROID CYTOMEL SYNTHROID THYROLAR-1 THYROLAR-1/2 THYROLAR-1/4 THYROLAR-2 THYROLAR-3 TIROSINT

Appendix G—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2013	**Short-Acting Beta Agonists** **Metered Dose Inhalers**	UF Class review Previously reviewed	▪ ProAir HFA	▪ None (ProAir HFA BCF)	▪ Proventil HFA ▪ Ventolin HFA ▪ levalbuterol (Xopenex HFA)	Pending signing of the minutes / 90 days	Quantity Limits apply see Formulary Search Tool	▪ None
May 2013	**Benign Prostatic Hypertrophy Drugs** **5-Alpha Reductase Inhibitor Subclass**	UF class review	▪ finasteride	▪ None (finasteride BCF)	▪ dutasteride (Avodart) ▪ dutasteride/tamsulosin (Jalyn)	Pending signing of the minutes / 60 days	Step therapy required – see comments	▪ Must try finasteride before Avodart in all new and current users; and, ▪ Must try finasteride before Jalyn in all new users. (See Appendix C)
Nov 2013	**Non-Insulin Diabetes Drugs** **DPP-4 Inhibitors Subclass** Previous reviews: Feb 2012, Aug 2012,and Aug 2013	New Drug in Already Reviewed Class alogliptin (Nesina) alogliptin/ metformin (Kazano) alogliptin/ pioglitazone (Oseni)	No change from previous review ▪ sitagliptin (Januvia) ▪ sitagliptin/metformin (Janumet) ▪ sitagliptin/ metformin ER (Janumet XR)	No change from previous review ▪ linagliptin (Tradjenta) ▪ linagliptin/metformin IR (Jentadueto) ▪ sitagliptin/simvastatin (Juvisync)	*Nov 2013* ▪ **alogliptin (Nesina)** ▪ **alogliptin/metformin (Kazano)** ▪ **alogliptin/pioglitazone (Oseni)** *Aug 2013* ▪ saxagliptin (Onglyza) ▪ saxagliptin/metformin ER (Kombiglyze XR)	Pending signing of minutes/ 60 days	Step therapy required – see comments	▪ Must try metformin and sulfonylurea first before any DPP-4 drug ▪ Must try sitagliptin-containing product first before Nesina, Kazano, Oseni, Tradjenta, Jentadueto, Onglyza, or Kombiglyze XR (See Appendix C)

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2013	**Osteoporosis Drugs** **Bisphosphonates Subclass** Previous review: June 2008, Nov 2011	New Drug in Already Reviewed Class	No change from previous review June 2008 ▪ alendronate ▪ alendronate with vitamin D ▪ ibandronate	No change from previous review June 2008 ▪ alendronate ▪ alendronate with vitamin D ▪ ibandronate ▪ risedronate IR (Actonel) ▪ risedronate IR with calcium (Actonel with Calcium)	*Nov 2013* ▪ **effervescent alendronate (Binosto)** Nov 2011 ▪ risedronate delayed release (Atelvia)	Pending signing of minutes/ 60 days	-	▪ None ▪ Section 703 drug-see Appendix E

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix H—Table of Abbreviations

5-ARIs	5-alpha reductase inhibitors
A1B	alpha-1 blocker
AS	ankylosing spondylitis
ASD(HA)	Assistant Secretary of Defense for Health Affairs
BCF	Basic Core Formulary
BIA	budget impact analysis
BPH	benign prostatic hypertrophy
CBC	complete blood count
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DCO	Defense Connect Online
DHA	Defense Health Agency
DoD	Department of Defense
DPP-4	dipeptidyl peptidase-4 inhibitors
EIB	exercise-induced bronchospasm
ER	extended release
FDA	U.S. Food and Drug Administration
HbA1c	hemoglobin A1c- lowering
HFA	hydrofluoroalkane
MDIs	metered-dose inhalers
MHS	Military Health System
MN	medical necessity
MS	multiple sclerosis
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
NF	nonformulary
P&T	Pharmacy and Therapeutics
PA	prior authorization
PORT	Pharmacy Outcomes Research Team
POS	points of service
PsA	psoriatic arthritis
QLs	quantity limits
SABAs	short-acting beta agonists
TIBs	targeted immunomodulatory biologics
TZD	thiazolidinedione
UF	Uniform Formulary

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2013

Second Addendum

I. UNIFORM FORMULARY (UF) DRUG CLASS REVIEWS—Self-Monitoring Blood Glucose System (SMBGS) Test Strips

The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips at the May 2013 P&T Committee meeting. The cost effectiveness, UF recommendation, Basic Core Formulary (BCF) recommendation, Prior Authorization (PA) criteria, Medical Necessity (MN) criteria, quantity limits (QLs), and implementation period were presented at the August 2013 P&T Committee meeting. An implementation period for the final decisions of 180 days, effective May 7, 2014, was approved by the Director, DHA, on November 7, 2013.

All steps necessary for implementation of the SMBGS test strips decisions were delayed 100 days, due to a GAO protest, which was dismissed on March 5, 2014. Due to the delay, the implementation period was extended to August 6, 2014, to allow for adequate time for DHA to send a letter to beneficiaries affected by the UF and PA decisions. Following dismissal of the GAO protest, a protest was filed in the Court of Federal Claims (CoFC). That protest has not yet been resolved and is not expected to be resolved until on or after August 20, 2014. Therefore, the effective date for implementation of the final SMBGS test strips decisions is postponed indefinitely, pending resolution of the CoFC protest. All steps necessary for implementation of the SMBG test strip decision remain on hold.

There is no change to the other decisions for the SMBGS test strips.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

31 Jul 2014
Date

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2013

Addendum

I. UNIFORM FORMULARY (UF) DRUG CLASS REVIEWS—Self-Monitoring Blood Glucose System (SMBGS) Test Strips

The Pharmacy and Therapeutics (P&T) Committee reviewed the clinical effectiveness of the SMBGS test strips at the May 2013 P&T Committee meeting. The cost effectiveness, Uniform Formulary (UF) recommendation, Basic Core Formulary (BCF) recommendation, Prior Authorization (PA) criteria, Medical Necessity (MN) criteria, quantity limits (QLs), and implementation period were presented at the August 2013 P&T Committee meeting. An implementation period for the final decisions of 180 days, effective May 7, 2014, was approved by the Director, DHA, on November 7, 2013.

All steps necessary for implementation of the SMBGS test strips decisions were delayed 100 days, due to a GAO protest, which was dismissed on March 5, 2014. Due to the delay, the implementation period is extended to August 6, 2014, to allow for adequate time for DHA to implement the decisions and to send a letter to beneficiaries affected by the UF and PA decisions. There is no change to the other decisions for the SMBGS test strips.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

29 Apr 2014
Date

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2013

I. UNIFORM FORMULARY DRUG CLASS REVIEWS

A. Corticosteroid Immune Modulators (Topical Steroids)

Background and Relative Clinical Effectiveness Conclusion—The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee evaluated the Corticosteroid Immune Modulators (Topical Steroids) Drug Class. The drugs were categorized into high- (classes 1 and 2), medium- (classes 3, 4, and 5), and low-potency agents (classes 6 and 7). Appendix B lists all products in the Topical Steroids Drug Class and their respective potency classifications, formulations, and generic availability.

Relative Clinical Effectiveness Conclusion—The full clinical effectiveness evaluation was presented at the May 2013 P&T Committee meeting. During the May 2013 meeting, the P&T Committee agreed (16 for, 0 opposed, 0 abstained, 1 absent) with the following conclusions:

- There is very limited generalizable data for all of the topical steroids. Heterogeneity of the data precludes direct and indirect comparisons. A product formulated for hair (e.g., foam, shampoo) from each potency class is desirable for inclusion on the UF.
- Safety issues are considered class effects.
- A Coopman Class C product (e.g., desoximetasone, clocortolone) is less likely to cause an allergic response, compared with Coopman Classes A (hydrocortisone, hydrocortisone acetate) and D1 (clobetasol, betamethasone, diflurasone, fluticasone, mometasone, aclometasone) agents, and is required for inclusion on the UF.
- For the high-potency topical steroids, none of the products offer unique advantages in terms of efficacy or safety over other agents in the high-potency class.
- The medium-potency topical steroid Pediaderm TA combination product co-packages triamcinolone with an emollient vehicle. There are no compelling advantages to using the co-packaged product versus using triamcinolone and a comparable emollient sold separately.

- For the low-potency topical steroids, there is no evidence to support clinically meaningful differences in efficacy or safety among the agents.
  - The Pediaderm HC combination product co-packages hydrocortisone with an emollient vehicle. There are no compelling advantages to using the co-packaged product versus using hydrocortisone and a comparable emollient sold separately.
  - Desonate Gel, Verdeso Foam, and Capex Shampoo all remain uniquely branded, without clinical advantages over the other generic low-potency topical steroids

Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis, including cost minimization analysis (CMA), was performed for the topical steroids within each potency class (high, medium, and low). CMA results showed that designating cost-effective agents from within each potency class as formulary on the UF yielded the most cost-effective results for the MHS.

The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 1 absent) that, for each topical steroid potency class, there were specific agents, strengths, and dosage forms determined to be cost-effective based on the weighted average cost per day of treatment across all three points of service (POS).

1. ***COMMITTEE ACTION: UNIFORM FORMULARY (UF) RECOMMENDATION***—The P&T Committee recommended (9 for, 3 opposed, 1 abstained, 1 absent) all topical steroid products be designated formulary on the UF, with the exception of the products listed below that are designated nonformulary (NF) (See Appendix H):
   - **Nonformulary High Potency products:** amcinonide 0.1% ointment (Cyclocort, generics); diflorasone 0.05% cream and ointment (Apexicon, generics); fluocinonide 0.1% cream (Vanos); halcinonide 0.1% cream and ointment (Halog);
   - **NF Medium Potency products:** amcinonide 0.1% cream and lotion (Cyclocort, generics); betamethasone valerate 0.12% foam (Luxiq, generics); clocortolone 0.1% cream (Cloderm); desonide 0.05% lotion (Desowen, generics); hydrocortisone probutate 0.1% cream (Pandel); hydrocortisone butyrate 0.1% cream and lotion (Locoid); triamcinolone with emollient #45, 0.1% cream kit (Pediaderm TA);
   - **NF Low Potency Products:** desonide 0.05% foam (Verdeso) and 0.05% gel (Desonate); fluocinolone 0.01% shampoo (Capex);

hydrocortisone with emollient #45, 2% lotion kit (Pediaderm HC).

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) maintaining fluocinonide 0.05% cream and triamcinolone acetate 0.1% cream on the BCF. Additionally, the P&T Committee recommended adding fluocinonide 0.05% ointment, clobetasol 0.05% cream, clobetasol 0.05% ointment, and triamcinolone acetate 0.1% ointment to the BCF.

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) MN criteria for all topical steroids that were designated as NF. (See Appendix D for full MN criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) TMA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

Director, DHA, Decision:  ☒Approved ☐ Disapproved

Approved, but modified as follows:

B. Self-Monitoring Blood Glucose System (SMBGS) Test Strips

Background and Relative Clinical Effectiveness—The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips. Appendix C lists the products in the SMBGS Test Strips Drug Class. Candidates for inclusion on the UF met all minimum required technical standards and U.S. Federal Government contracting requirements.

Relative Clinical Effectiveness Conclusion—The full clinical effectiveness evaluation was presented at the May 2013 P&T Committee meeting. During the May 2013 meeting, the P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following for the SMBGS test strips.

- *U.S. Federal Government contracting requirements*: SMBGS test strips eligible for inclusion on the UF must be available at all three POS and must be compliant with the Trade Agreements Act. Corresponding SMBGS glucometers must also

be compliant with the Trade Agreements Act. Manufacturers of SMBGS glucometers will be required to provide DoD beneficiaries with a no-cost glucometer.

- *Minimum technical requirements*: Candidate SMBGS test strips eligible for inclusion on the UF must meet minimum technical requirements in the areas of accuracy, sample size, alternate site testing, result time, memory capacity, ease of use, customer support, downloading capabilities, and data management capabilities. See pages 15-16 for detailed technical requirements. During the August 2013 meeting, newly proposed ISO standards were presented to the P&T Committee. However, the current 2003 ISO 15197 standard remains effective and there is no change regarding this minimum technical requirement.
- *SMBG strips meeting the final technical and U.S. Federal Government contracting requirements*: The SMBG test strips meeting the final technical and U.S. Federal Government contracting requirements are FreeStyle Lite (Abbott), FreeStyle InsuLinx (Abbott), Precision Xtra (Abbott); ACCU-CHEK Aviva Plus (Roche); CONTOUR NEXT (Bayer); TRUEtest (Nipro Diagnostics); Nova Max (Nova); Glucocard 01-Sensor (Arkray), Glucocard Vital (Akray); and Prodigy No Coding (Prodigy).
- *Overall relative clinical effectiveness conclusion:* The Committee concluded that any of the 10 final SMBGS test strip candidates were acceptable for inclusion on the UF. There are no clinically relevant differences between the 10 SMBGS test strips meeting the final technical and U.S. Federal Government contracting requirements set forth by the P&T Committee.

Relative Cost-Effectiveness Analysis and Conclusion—The P&T Committee concluded (12 for, 0 opposed, 0 abstained, 2 absent) the Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra) were the most cost-effective SMBGS products, based on the weighted average cost per strip across all three POS, followed by (ranked in order from most cost effective to least cost effective) Arkray (GLUCOCARD 01-SENSOR, GLUCOCARD Vital), Bayer (CONTOUR NEXT), Nipro (TRUEtest), Roche (ACCU-CHEK Aviva Plus), Prodigy (Prodigy No Coding), and Nova (Nova Max) products.

Among the formulary options evaluated, CMA and budget impact analysis (BIA) results showed the most cost-effective scenario designated Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra) as the UF step-preferred test strip "suite" with all other SMBGS test strips designated NF and non-preferred, where all current and new users are required to first try an Abbott test strip.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) the following:
    - Formulary and step-preferred on the UF:
        - Precision Xtra (Abbott)
        - FreeStyle Lite (Abbott)
        - FreeStyle InsuLinx (Abbott)
    - Nonformulary and non-step preferred on the UF:
        - ACCU-CHEK Aviva Plus (Roche)
        - GLUCOCARD 01-Sensor (Arkray)
        - GLUCOCARD Vital (Arkray)
        - CONTOUR NEXT (Bayer)
        - NovaMax (Nova)
        - TRUEtest (Nipro Diagnostics)
        - Prodigy No Coding (Prodigy)
        - One Touch Verio
        - One Touch Ultra
        - All other test strips listed in Appendix C (with the exception of FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra)
    - This recommendation includes step therapy, which requires a trial of one of the Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, or Precision Xtra) prior to use of a nonformulary test strip in all current and new users of a nonformulary test strip.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) designating FreeStyle Lite (Abbott) with BCF status, based on clinical and cost-effectiveness, and removing Precision Xtra (Abbott) from the BCF. Note: Precision Xtra (Abbott) is designated with Uniform Formulary status and is step-preferred on the UF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1abstained, 1 absent) manual PA criteria for all new and current users of a nonformulary SMBG test strip, requiring a trial of FreeStyle Lite, FreeStyle InsuLinx, or Precision Xtra prior to the use of a nonformulary SMBG test strip. (See Appendix E for full criteria).

4 ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs/days

supply limits for the SMBGS test strips, limiting use to 150 strips/30-day supply in the Retail Network, and 450 strips/90-day supply via Mail Order.

5. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) MN criteria for the NF SMBGS test strips. (See Appendix D for full MN criteria.)

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD*** The P&T Committee recommended (11 for, 1 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 120-day implementation period in all POS; and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is March 12, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

Considering the comments of the Beneficiary Advisory Panel, implementation period is 180 days. Effective date is May 7, 2014.

II. UTILIZATION MANAGEMENT

A. Prior Authorizations

1. **Injectable Corticotropin (HP Acthar Gel)**— The P&T Committee established manual PA criteria for all new and current users of HP Acthar Gel, limiting use to infantile spasms (West Syndrome) for patients less than 24 months old at initiation of treatment and not previously treated with corticotropin. Additional uses for acute exacerbations of multiple sclerosis and/or optic neuritis, acute gout, and protein-wasting nephropathies may be permitted on appeal.

   The following uses for Acthar Gel are considered unsupportable: dermatomyositis, polymyositis, psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis and ankylosing spondylitis), sarcoidosis, serum sickness, Stevens-Johnson Syndrome (severe erythema multiforme), and systemic lupus erythematosis.

   a) ***COMMITTEE ACTION: HP ACTHAR GEL PA CRITERIA*** The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) manual PA criteria for all current and new users of HP Acthar

Gel, limiting use to the specific FDA-approved indication of infantile spasms (West Syndrome). Prior Authorization will expire after 30 days for infantile spasms; retreatment is not covered. Use for acute exacerbations of multiple sclerosis and/or optic neuritis, acute gout, and protein-wasting nephropathies will be on appeal only. Other uses of HP Acthar Gel are considered unsupportable and not covered. (See Appendix E for full criteria.)

b) ***COMMITTEE ACTION: HP ACTHAR GEL PA IMPLEMENTATION***—The P&T Committee recommended (8 for, 3 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 30-day implementation period in all POS; and 2) TMA send a letter to beneficiaries affected by this PA decision. Based on the P&T Committee's recommendation, the effective date is December 11, 2013.

2. **Doxylamine/Pyridoxine (Diclegis)**—Diclegis contains 10 mg of doxylamine and 10 mg of pyridoxine and is FDA-approved for treating pregnant women experiencing nausea and vomiting.

   a) ***COMMITTEE ACTION: PYRIDOXINE/DOXYLAMINE (DICLEGIS) PA CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) that manual PA criteria apply to new users of Diclegis who are being treated for nausea and vomiting during pregnancy. The PA will expire after nine months. (See Appendix E for full criteria.)

   b) ***COMMITTEE ACTION: PYRIDOXINE/DOXYLAMINE (DICLEGIS) PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

3. **Targeted Immunomodulatory Biologics: Ustekinumab (Stelara) and Golimumab (Simponi)**—PA criteria currently apply to the Targeted Immunomodulatory Biologics (TIBs). Ustekinumab was previously limited to injection by health care professionals, but is now available in pre-filled syringes labeled for patient self administration for treatment of plaque psoriasis. Also, the FDA recently approved a new indication for golimumab for treatment of moderate to severe ulcerative colitis.

a) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI) PA CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) PA criteria for ustekinumab for plaque psoriasis and golimumab for ulcerative colitis, consistent with the products' labeling. (See Appendix E for full criteria.)

b) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

B. Quantity Limits

1. **Targeted Immunomodulatory Biologics: Ustekinumab (Stelara) and Golimumab (Simponi)**—QLs currently apply to the TIBs. The P&T Committee evaluated QLs for ustekinumab for the new indication of plaque psoriasis for patient self administration, and for golimumab for the new indication of ulcerative colitis.

   a) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI) QLs***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs for Stelara and Simponi, as outlined in Appendix F, consistent with FDA-approved product labeling.

2. **Oral Chemotherapy Drugs: Dabrafenib (Tafinlar), Trametinib (Mekinist), and Afatinib (Glotrif)**—The P&T Committee evaluated QLs for several oral chemotherapy drugs, including dabrafenib (Tafinlar), indicated for treatment of treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations; trametinib (Mekinist) for treatment of unresectable or metastatic melanoma with BRAF V600E mutations; and afatinib (Glotrif) for first-line treatment of metastatic non-small cell lung cancer whose tumors have specific mutations. QLs exist for several other oral chemotherapy agents.

   a) ***COMMITTEE ACTION: TAFINLAR, MEKINST, AND GLOTRIF QLs***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs for dabrafenib (Tafinlar), trametinib (Mekinist), and afatinib (Glotrif) as outlined in Appendix F, consistent with FDA-approved product labeling.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

III. Fiscal Year 2008 National Defense Authorization Act, Section 703

A. Section 703—The P&T Committee reviewed drugs from manufacturers that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not compliant with Fiscal Year 2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the Retail POS and medical necessity in MTFs. These NF drugs will remain available in the Mail Order POS without pre-authorization.

1. ***COMMITTEE ACTION: DRUGS DESIGNATED NF***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) to designate the products in Appendix G (listed by manufacturer) as nonformulary on the Uniform Formulary.

2. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) the following Pre-Authorization Criteria for the drugs listed as nonformulary in Appendix G: 1) obtaining the product from home delivery would be detrimental to the patient; and 2) for branded products with AB generic availability, use of the generic product would be detrimental to the patient. These pre-authorization criteria do not apply to any point of service other than retail network pharmacies.

3. ***COMMITTEE ACTION: UF AND PRE-AUTHORIZATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and 2) TMA send a letter to beneficiaries affected by the these decisions. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

Patriot Pharmaceuticals has now signed a pricing agreement for all of its covered drugs. Qutenza patch and Zyclara cream are also now covered by a pricing agreement. Therefore, the Patriot Pharmaceuticals products listed in Appendix G, Qutenza patch, and Zyclara cream are excluded from this action.

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH
Lieutenant General, USAF, MC, CFS
Director

7 NOV 2013
Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

August 2013

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 14 and 15, 2013, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May Minutes**—Jonathon Woodson M.D., Director, TRICARE® Management Activity (TMA), approved the minutes for the May 2013 DoD P&T Committee meeting on August 6, 2013.
2. **Changes to the May 2013 Minutes:**
    a) **Emergency Contraceptives**—The Director's decision was that due to over-the-counter availability of levonorgestrel 1.5 mg (Plan B One-Step) without age restrictions, no emergency contraceptives shall be included on the Basic Core Formulary (BCF). However, Military Treatment Facilities (MTFs) shall carry Plan B One-Step and provide it no cost.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and BCF recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. UF DRUG CLASS REVIEWS

A. Corticosteroid Immune Modulators (Topical Steroids)

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the Corticosteroid Immune Modulators (Topical Steroids) Drug Class. The drug

class is comprised of 22 individual chemical entities, available in over 100 different formulations and vehicles. The Stoughton-Cornell classification system, which divides the drugs into seven classes based on their vasoconstrictive properties, was used to further divide the drugs into high- (classes 1 and 2), medium- (classes 3, 4, and 5), and low-potency agents (classes 6 and 7). Over-the-counter (OTC) products are excluded from the class. Appendix B lists all products in the Corticosteroid Immune Modulators (Topical Steroids) Drug Class and their respective potency classifications, formulations, and generic availability.

Relative Clinical Effectiveness Conclusion—The full clinical effectiveness evaluation was presented at the May 2013 P&T Committee meeting. During the May 2013 meeting, the P&T Committee agreed (16 for, 0 opposed, 0 abstained, 1 absent) with the following conclusions:

- For all of the topical steroids, there is very limited generalizable data. Heterogeneity of the data precludes direct and indirect comparisons. A product formulated for hair (e.g., foam, shampoo) from each potency class is desirable for inclusion on the UF.
- Safety issues are considered class effects.
- A Coopman Class C product (e.g., desoximetasone, clocortolone) is less likely to cause an allergic response, compared with Coopman Classes A (hydrocortisone, hydrocortisone acetate) and D1 (clobetasol, betamethasone, diflurasone, fluticasone, mometasone, aclometasone) agents, and is required for inclusion on the UF.
- For the high-potency topical steroids, none of the products offer unique advantages in terms of efficacy or safety over other agents in the high-potency class.
    - Clobetasol is offered in more vehicles and is more extensively studied than the other high-potency products.
    - Fluocinonide was frequently mentioned as required for inclusion on the UF in a survey of Military Health System (MHS) providers.
    - Flurandrenolide tape has several unique therapeutic uses.
    - Clobetasol, halobetasol, augmented betamethasone dipropionate, and fluocinonide 1% cream products have package-labeled weekly exposure limits.
- For the medium-potency topical steroids, the following conclusions were made:
    - Triamcinolone is offered in more vehicles, is more extensively studied, and more frequently mentioned as required for inclusion on the UF in the MHS

provider survey than the other medium-potency agents. It has a modest risk of skin atrophy.

- Triamcinolone (Kenalog Spray) is the only spray product in the medium-potency class.
- The Pediaderm TA combination product co-packages triamcinolone with an emollient vehicle. There are no compelling advantages to using the co-packaged product versus using triamcinolone and a comparable emollient sold separately.
- There is weak evidence that clocortolone may have less risk of hypothalamic-pituitary-adrenal axis suppression than other medium- potency steroids.
- Hydrocortisone butyrate and fluticasone propionate are the only medium-potency agents labeled for use in children as young as three months of age.
- Fluticasone propionate, mometasone, and prednicarbate have the most favorable therapeutic indices among the medium-potency steroids.
- Desonide ointment and lotion, betamethasone valerate, and hydrocortisone valerate were frequently favorably mentioned in the MHS provider survey as required for inclusion on the UF.

- For the low-potency topical steroids, there is no evidence to support clinically meaningful differences in efficacy or safety among the agents.
  - Hydrocortisone was more frequently favorably mentioned in the MHS provider survey than the other low-potency agents.
  - The Pediaderm HC combination product co-packages hydrocortisone with an emollient vehicle. There are no compelling advantages to using the co-packaged product versus using hydrocortisone and a comparable emollient sold separately.
  - Derma-Smoothe/FS, a fluocinolone acetonide shampoo product, has the theoretical risk of inducing a peanut allergy.
  - Desonate Gel, Verdeso Foam, and Capex Shampoo all remain uniquely branded, without clinical advantages over the other generic low-potency topical steroids.

Relative Cost-Effectiveness Analysis and Conclusion—A pharmacoeconomic analysis, including cost minimization analysis (CMA), was performed for the topical steroids within each potency class (high, medium, and low). CMA results showed that designating cost-effective agents from within each potency class as formulary on the UF yielded the most cost-effective results for the MHS.

The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 1 absent) that, for each topical steroid potency class, there were specific agents, strengths, and dosage forms determined to be cost-effective based on the weighted average cost per day of treatment across all three points of service (POS).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (9 for, 3 opposed, 1 abstained, 1 absent) all topical steroid products be designated formulary on the UF, with the exception of the products listed below that are designated NF (See Appendix G):

    - **NF High Potency products:** amcinonide 0.1% ointment (Cyclocort, generics); diflorasone 0.05% cream and ointment (Apexicon, generics); fluocinonide 0.1% cream (Vanos); halcinonide 0.1% cream and ointment (Halog);

    - **NF Medium Potency products:** amcinonide 0.1% cream and lotion (Cyclocort, generics); betamethasone valerate 0.12% foam (Luxiq, generics); clocortolone 0.1% cream (Cloderm); desonide 0.05% lotion (Desowen, generics); hydrocortisone probutate 0.1% cream (Pandel); hydrocortisone butyrate 0.1% cream and lotion (Locoid); triamcinolone with emollient #45, 0.1% cream kit (Pediaderm TA);

    - **NF Low Potency products:** desonide 0.05% foam (Verdeso) and 0.05% gel (Desonate); fluocinolone 0.01% shampoo (Capex); hydrocortisone with emollient #45, 2% lotion kit (Pediaderm HC).

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) maintaining fluocinonide 0.05% cream and triamcinolone acetate 0.1% cream on the BCF. Additionally, the P&T Committee recommended adding fluocinonide 0.05% ointment, clobetasol 0.05% cream, clobetasol 0.05% ointment, and triamcinolone acetate 0.1% ointment to the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) MN criteria for all topical steroids that were designated as NF. (See Appendix D for full MN criteria.)

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and, 2) TMA send a letter to beneficiaries affected by the UF decision. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

B. Self-Monitoring Blood Glucose System (SMBGS) Test Strips

Background and Relative Clinical Effectiveness—The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips, including the attributes of the test strips and glucometers. The SMBGS test strips were previously reviewed for UF placement in August 2008. The primary goal for this review is to ensure uniform availability of quality SMBGS test strips across the MHS (MTF, Retail, and Mail Order POS). SMBGS glucometers are not included as part of the TRICARE outpatient pharmacy benefit (they are included under the medical benefit) and are not the focus of the review; however, provisions have been made to provide SMBGS glucometers at no cost to MHS beneficiaries. Appendix C lists the products in the SMBGS Test Strips Drug Class.

The FDA classifies SMBGS test strips and glucometers as medical devices, rather than drugs, thus the focus of the clinical effectiveness review centers on differences in the technical aspects/attributes among the products. Candidates for inclusion on the UF must meet all minimum required technical standards and U.S. Federal Government contracting requirements. The P&T Committee reviewed the existing technical requirements approved in May 2007, and recommended updates to the criteria.

Relative Clinical Effectiveness Conclusion—The full clinical effectiveness evaluation was presented at the May 2013 P&T Committee meeting. During the May 2013 meeting, the P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following for the minimum technical requirements and U.S. Federal Government contracting requirements for the SMBGS test strips.

- *U.S. Federal Government contracting requirements*: SMBGS test strips eligible for inclusion on the UF must be available at all three POS and must be compliant with the Trade Agreements Act. Corresponding SMBGS glucometers must also be compliant with the Trade Agreements Act. Manufacturers of SMBGS glucometers will be required to provide DoD beneficiaries with a no-cost glucometer.
- *Minimum technical requirements*: Candidate SMBGS test strips eligible for inclusion on the UF must meet the following minimum technical requirements:
    - Accuracy: must meet FDA standards for accuracy based on the International Organization for Standardization (ISO) 15197 guidelines. During the August 2013 meeting, newly proposed ISO standards were

presented to the P&T Committee. However, the current 2003 ISO 15197 standard remains effective and there is no change regarding this minimum technical requirement.

- Sample size of $\leq$ 1 microliter
- Alternate site testing: more than one alternate site approved.
- Result time: $\leq$ 10 seconds
- Memory capacity: $\geq$ 250 readings
- Ease of use: glucometer must be easy to code/calibrate, have a large visual display, and be easy to handle for patients with dexterity issues.
- Customer support: 24-hour helpline available, for beneficiaries residing outside the continental United States.
- Downloading capabilities: results must be downloadable
- Data management capabilities: data management capabilities required (e.g., software, cloud computing).

- *SMBG strips meeting the final technical and U.S. Federal Government contracting requirements*: The SMBG test strips meeting the final technical and U.S. Federal Government contracting requirements are Abbott FreeStyle Lite, Abbbot FreeStyle InsuLinx, Abbott Precision Xtra; Roche ACCU-CHEK Aviva Plus; Bayer CONTOUR NEXT; Nipro Diagnostics TRUEtest; Nova Nova Max; Arkray Glucocard 01-Sensor, Akray Glucocard Vital; and Prodigy Prodigy No Coding.
- *MHS Provider Opinion*: MTF and Managed Care Support Contractors (MCSCs) were surveyed for their opinions on the SMBGS test strips and glucometers. The majority of the respondents ranked meter accuracy as the most important attribute. The majority of MTF respondents stated one glucometer was adequate to meet their needs, while the MCSCs requested availability of more than one glucometer to allow the patient options.
- *Overall relative clinical effectiveness conclusion:* The Committee concluded that any of the 10 final SMBGS test strip candidates were acceptable for inclusion on the UF. There are no clinically relevant differences between the 10 SMBGS test strips meeting the final technical and U.S. Federal Government contracting requirements set forth by the P&T Committee.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and budget impact analysis (BIA) were performed for SMBGS test strips that met all minimum required technical standards and U.S. Federal Government contracting requirements. CMA was performed for the following manufacturer's products: Abbott (FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra), Roche (ACCU-CHEK Aviva Plus), Bayer

(CONTOUR NEXT), Nipro Diagnostics (TRUEtest), Nova (Nova Max), ARKRAY (GLUCOCARD 01-SENSOR, GLUCOCARD Vital), and Prodigy (Prodigy No Coding) test strips. For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted.

The P&T Committee concluded (12 for, 0 opposed, 0 abstained, 2 absent) the Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra) were the most cost-effective SMBGS products, based on the weighted average cost per strip across all three POS, followed by (ranked in order from most cost effective to least cost effective). Arkray (GLUCOCARD 01-SENSOR, GLUCOCARD Vital), Bayer (CONTOUR NEXT), Nipro (TRUEtest), Roche (ACCU-CHEK Aviva Plus), Prodigy (Prodigy No Coding), and Nova (Nova Max) products.

Among the formulary options evaluated, CMA and BIA results showed the most cost-effective scenario designated Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra) as the UF step-preferred test strip "suite" with all other SMBGS test strips designated NF and non-preferred, where all current and new users are required to first try an Abbott test strip.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) the following:
    - Formulary and step-preferred on the UF:
        - Precision Xtra (Abbott)
        - FreeStyle Lite (Abbott)
        - FreeStyle InsuLinx (Abbott)
    - Nonformulary and non-step preferred on the UF:
        - ACCU-CHEK Aviva Plus (Roche)
        - GLUCOCARD 01-Sensor (Arkray)
        - GLUCOCARD Vital (Arkray)
        - CONTOUR NEXT (Bayer)
        - NovaMax (Nova)
        - TRUEtest (Nipro Diagnostics)
        - Prodigy No Coding (Prodigy)
        - One Touch Verio
        - One Touch Ultra
        - All other test strips listed in Appendix C (with the exception of FreeStyle Lite, FreeStyle InsuLinx, Precision Xtra)
    - This recommendation includes step therapy, which requires a trial of one of the Abbott test strips (FreeStyle Lite, FreeStyle InsuLinx, or

Precision Xtra) prior to use of a nonformulary test strip in all current and new users of a nonformulary test strip.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) designating FreeStyle Lite (Abbott) with BCF status, based on clinical and cost-effectiveness, and removing Precision Xtra (Abbott) from the BCF. Note: Precision Xtra (Abbott) is designated with Uniform Formulary status and is step-preferred on the UF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1abstained, 1 absent) manual PA criteria for all new and current users of a nonformulary SMBG test strip, requiring a trial of FreeStyle Lite, FreeStyle InsuLinx, or Precision Xtra prior to the use of a nonformulary SMBG test strip. (See Appendix E for full criteria).

4 ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs/days supply limits for the SMBGS test strips, limiting use to 150 strips/30-day supply in the Retail Network, and 450 strips/90-day supply via Mail Order.

5. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 1 absent) MN criteria for the NF SMBGS test strips. (See Appendix D for full MN criteria.)

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD*** The P&T Committee recommended (11 for, 1 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 120-day implementation period in all POS; 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is March 12, 2014.
See p 6. Considering the commentsof the Beneficiary Advisory Panel, implementation period is 180 days.

V. UTILIZATION MANAGEMENT

A. PAs

1. **Injectable Corticotropin (HP Acthar Gel)**—Injectable corticotrophin has been commercially available since 1952, but now is only marketed as a proprietary product, HP Acthar Gel. The P&T Committee established manual PA criteria for all new and current users of HP Acthar Gel, limiting use to infantile spasms (West Syndrome) for patients less than 24 months

old at initiation of treatment and not previously treated with corticotropin. Additional uses for acute exacerbations of multiple sclerosis and/or optic neuritis, acute gout, and protein-wasting nephropathies may be permitted on appeal.

The following uses for Acthar Gel are considered unsupportable: dermatomyositis, polymyositis, psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis and ankylosing spondylitis), sarcoidosis, serum sickness, Stevens-Johnson Syndrome (severe erythema multiforme), and systemic lupus erythematosis.

a) ***COMMITTEE ACTION: HP ACTHAR GEL PA CRITERIA***
The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) manual PA criteria for all current and new users of HP Acthar Gel, limiting use to the specific FDA-approved indication of infantile spasms (West Syndrome). Prior Authorization will expire after 30 days for infantile spasms; retreatment is not covered. Use for acute exacerbations of multiple sclerosis and/or optic neuritis, acute gout, and protein-wasting nephropathies will be on appeal only. Other uses of HP Acthar Gel are considered unsupportable. (See Appendix E for full criteria.)

b) ***COMMITTEE ACTION: HP ACTHAR GEL PA IMPLEMENTATION***—The P&T Committee recommended (8 for, 3 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this PA decision. Based on the P&T Committee's recommendation, the effective date is December 11, 2013.

2. **Doxylamine/Pyridoxine (Diclegis)**—Diclegis contains 10 mg of doxylamine and 10 mg of pyridoxine and is FDA-approved for treating pregnant women experiencing nausea and vomiting. The P&T Committee recommended manual PA criteria for all new users of Diclegis. Diclegis is limited to use for management of nausea and vomiting during pregnancy (NVP) and excluded for the treatment of hyperemesis gravidarum. Patients must have tried at least one nonpharmacologic treatment (e.g., ginger, acupressure, high-protein bedtime snack) and OTC pyridoxine. An alternate antiemetic (e.g., ondansetron) should be considered prior to Diclegis.

   a) ***COMMITTEE ACTION: PYRIDOXINE/DOXYLAMINE (DICLEGIS) PA CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) that manual PA criteria apply to new users of

Diclegis who are being treated for nausea and vomiting during pregnancy. The PA will expire after nine months. (See Appendix E for full criteria.)

b) ***COMMITTEE ACTION: PYRIDOXINE/DOXYLAMINE (DICLEGIS) PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

3. **Targeted Immunomodulatory Biologics: Ustekinumab (Stelara) and Golimumab (Simponi)**—PA criteria currently apply to the Targeted Immunomodulatory Biologics (TIBs). Ustekinumab was previously limited to injection by health care professionals, but is now available in pre-filled syringes labeled for patient self administration for treatment of plaque psoriasis. Also, the FDA recently approved a new indication for golimumab for treatment of moderate to severe ulcerative colitis.

   a) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI) PA CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) PA criteria for ustekinumab for plaque psoriasis and golimumab for ulcerative colitis, consistent with the products' labeling. (See Appendix E for full criteria.)

   b) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

B. QLs

1. **Targeted Immunomodulatory Biologics: Ustekinumab (Stelara) and Golimumab (Simponi)**—QLs currently apply to the TIBs. The P&T Committee evaluated QLs for ustekinumab for the new indication of plaque psoriasis for patient self administration, and for golimumab for the new indication of ulcerative colitis.

a) ***COMMITTEE ACTION: USTEKINUMAB (STELARA) AND GOLIMUMAB (SIMPONI) QLs***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs for Stelara and Simponi, as outlined in Appendix F, consistent with FDA-approved product labeling.

2. **Oral Chemotherapy Drugs: Dabrafenib (Tafinlar), Trametinib (Mekinist), and Afatinib (Glotrif)**—The P&T Committee evaluated QLs for several oral chemotherapy drugs, including dabrafenib (Tafinlar), indicated for treatment of treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations; trametinib (Mekinist) for treatment of unresectable or metastatic melanoma with BRAF V600E mutations; and afatinib (Glotrif) for first-line treatment of metastatic non-small cell lung cancer whose tumors have specific mutations. QLs exist for several other oral chemotherapy agents.

a) ***COMMITTEE ACTION: TAFINLAR, MEKINST, AND GLOTRIF QLs***—The P&T Committee recommended (11 for, 0 opposed, 1 abstained, 2 absent) QLs for dabrafenib (Tafinlar), trametinib (Mekinist), and afatinib (Glotrif) as outlined in Appendix F, consistent with FDA-approved product labeling.

VI. SECTION 703

A. Section 703—The P&T Committee reviewed drugs from manufacturers that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not compliant with Fiscal Year 2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the Retail POS and medical necessity in MTFs. These NF drugs will remain available in the Mail Order POS without pre-authorization.

1. ***COMMITTEE ACTION: DRUGS DESIGNATED NF***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) to designate the products in Appendix G (listed by manufacturer) as nonformulary on the Uniform Formulary

2. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) the following Pre-Authorization Criteria for the drugs listed as nonformulary in Appendix G: 1) Obtaining the product from the home delivery would be detrimental to the patient and 2) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

These pre-authorization criteria do not apply to any point of service other than retail network pharmacies.

3. ***COMMITTEE ACTION: UF AND PRE-AUTHORIZATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 3 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS; and 2) TMA send a letter to beneficiaries affected by the these decisions. Based on the P&T Committee's recommendation, the effective date is January 8, 2014.

See p 10. Patriot Pharmaceuticals has now signed a pricing agreement for all of its covere drugs. Qutenza patch and Zyclara cream are excluded from this action.

VII. OVERVIEWS

Overviews of the following four drug class were presented to the P&T Committee: the Inhaled Corticosteroids/Long-Acting Beta Agonists, the Inhaled Short-Acting Beta Agonists, the Antilipidemic-1 Agents (LIP-1s), and the Benign Prostatic Hyperplasia drugs comprised of the 5-alpha-reductase inhibitors and alpha blockers. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in contract solicitation, and for completing the clinical effectiveness reviews and developing the appropriate cost-effectiveness models. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

VIII. ITEMS FOR INFORMATION

A. Bulk Chemicals In Compounded Medications—The P&T Committee was presented with an update and will be given a full presentation at an upcoming meeting.

B. FY13 TRICARE Pharmacy Copayments—The P&T Committee was briefed on the initial impact of new pharmacy copayments implemented in February 2013 on pharmaceutical utilization in the Military Health System. The analysis included the first 5 months of data following copayment increases for Tier 2 products (preferred brands) and Tier 3 products (non-preferred brands) in the Retail Network and at Mail Order. The results showed preliminary evidence that the increase in copays (from $25 to $43 in Mail Order/$44 in the Retail Network) for Tier 3 medications appeared to be associated with declining use of these products, with about a 10% reduction over the first 5 months. However, the new copays did not appear to be associated with any major changes in use of medications overall (i.e., across all Tiers). Additional updates will be provided to the P&T Committee as data becomes available.

C. Angiotensin Receptor Blockers (ARBs)/Direct Renin Inhibitor—The P&T committee considered the merits of formulary action in the Angiotensin Receptor Blockers, Direct Renin Inhibitors and respective fixed dose combination products drug

classes. Based on current pricing agreements and pending availability of new generic entrants, the P&T committee opted not to take any formulary action at this time.

D. **Prior Authorization (PA) Implementation date for canagliflozin (Invokana)**—The implementation date for PA criteria applicable to canagliflozin (Invokana) was changed to September 25, 2013.

IX. ADJOURNMENT

The meeting adjourned at 1015 hours on August 15, 2013. The next meeting will be in November 2013.

Appendix A—Attendance: August 2013 P&T Committee Meeting

Appendix B—Corticosteroid Immune Modulators (Topical Steroids) Drug Class

Appendix C—Self-Monitoring Blood Glucose System Test Strips Products in Class

Appendix D—Table of Medical Necessity

Appendix E—Table of Prior Authorization Criteria

Appendix F—Table of Quantity Limits

Appendix G—Table of Drugs Designated NF due to Section 703

Appendix H—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix I—Table of Abbreviations

Appendix A—Attendance: August 2013 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL John Spain, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CDR Brian King, MC	Navy, Internal Medicine Physician
LTC Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
LCDR Tiffany Scott, MSC, via DCO	Defense Logistics Agency Troop Support
Capt Richard Caballero, via DCO	Defense Logistics Agency Troop Support
Capt Randall Sweeney, via DCO	Defense Logistics Agency Troop Support
Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
CDR Matthew Baker, USPHS, by phone	Indian Health Service
CAPT Jamie Kersten	Navy Medicine Training Support Center
LCDR David Sohl	University of Texas Masters Student

Appendix A—Attendance (continued)

Others Present	
LTC Chris Conrad, MS	DoD Pharmacoeconomic Center
LCDR Marisol Martinez, USPHS	DoD Pharmacoeconomic Center
LCDR Joshua Devine, USPHS	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
LCDR Linh Quach, MSC	DoD Pharmacoeconomic Center
Lt Col Melinda Henne, MC	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
LT Kendra Jenkins, USPHS	DoD Pharmacoeconomic Center
HM1 Nichole Moraldo	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo via DCO	DoD Pharmacoeconomic Center
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Mr. Kirk Stocker	DoD Pharmacy Outcomes Research Team contractor
Andrew Delgado	University of Texas Health Science Center/University of Texas College of Pharmacy Student
Yuna Bae via DCO	University of Maryland School of Pharmacy Student
Christopher Bender via DCO	Lake Erie College of Osteopathic Medicine School of Pharmacy Student

Appendix B—Corticosteroid Immune Modulators (Topical Steroids) Drugs in the Class (For UF decision see Appendix H)

Generic	Brand Generic	Strengths & formulations	Patent Exp
High-Potency Steroids (Classes 1 and 2)			
Clobetasol Propionate	Clobex Temovate/-E Olux/-E Generics: Yes (lotion/ointment/solution/ shampoo/ ointment/gel/foam)	0.05% Lotion, Shampoo, Spray 0.05% Oint, Soln, Gel, Cream 0.05% Foam 0.05% Ointment, Soln, Gel, Cream 0.05% Cream	9/2017–6/2019 -- 3/2016–9/2019 -- -- --
Diflorasone diacetate	*Psorcon/-E; Apexicon E** Generic: Yes	0.05% Ointment 0.05% Cream 0.05% Cream with Emollient	-- -- --
Halobetasol propionate	*Halac, Halonate, Halonate PAC** Ultravate/-PAC Generics: Yes	0.05% Cream, Ointment, Foam Combinations with Lactates	-- --
Flurandrenolide	Cordran Generics: No	4mcg/sq cm Tape	--
Desoximetasone	Topicort Generics: Yes	0.25% Cream, Ointment, Spray 0.05% Gel	-- --
Fluocinonide/-Emollient	Vanos, *Lidex/-E** Generics: Yes	0.1% Cream 0.05% Gel, Cream, Oint, Soln	-- --
Halcinonide	Halog Generics: Halog is generic	0.1% Cream, Ointment	--
Betamethasone dipropionate augmented	Diprolene/-AF Generics: Yes	0.05% Cream, Lotion, Ointment 0.05% Gel (generic only)	
Amcinonide	Cyclocort Generics: Yes	0.1% Ointment	--

*** Italicized medications are branded products (reference listed drugs) that are not currently marketed.**

Appendix B—Corticosteroid Immune Modulators (Topical Steroids) Drugs in the Class (For UF decision see Appendix H)

Generic	Brand Generic	Strengths & formulations	Patent Exp
Medium-Potency Steroids (Classes 3, 4, 5)			
Amcinonide	Cyclocort Generics: Yes	0.1% Cream, Lotion	
Betamethasone dipropionate	Diprosone Generics: Yes	0.05% Cream 0.05% Lotion (generic only)	--
Betamethasone valerate	Beta-Val, Luxiq, Valisone Generics: Yes (ointment)	0.1% Cream, Lotion 0.12% Foam	Luxiq: 3/2016–5/2017 --
Clocortalone pivalate	Cloderm Generics: No	0.1% Cream	--
Desonide	Desowen Generics: Yes	0.05% Ointment, Lotion	--
Desoximetasone	Topicort Generics: Yes	0.05% Cream	--
Fluocinolone	Synalar Generics: Yes (cream/ointment)	0.025% Cream	--
Flurandrenolide	Cordran Generics: No	0.05% Cream, Lotion	--
Fluticasone propionate	Cutivate Generics: Yes	0.05% Cream, Lotion 0.005% Ointment	--
Hydrocortisone butyrate	Locoid Locoid Lipocream Generics: Yes (lotion/ointment/solution)	0.1% Cream (brand only), Ointment, Solution, Lotion 0.1% Cream	Lotion: 1/2025–12/2026 Cream: 6/2014
Hydrocortisone probutate	Pandel Generics: No	0.1% Cream	--
Hydrocortisone valerate	Brand: *Westcort** Generics: Yes	0.2% Cream, Ointment	--
Mometasone furoate	Elocon Generics: Yes	0.1% Ointment, Cream, Solution	--
Prednicarbate	Dermatop Generics: Yes	0.1% Cream, Ointment	--
Triamcinolone acetate	Aristocort HP Kenalog Trianex Kenalog Triderm Triacet Generics: Yes (cream/ointment/lotion)	0.5% Cream 0.025%, 0.1%, 0.5% Cream 0.025%, 0.1% Lotion 0.025%; 0.1% Ointment 0.147 mg/g Topical Spray 0.1% Cream 0.05% Ointment	-- -- -- -- -- -- --
Triamcinolone Acetonide	Aristocort A Pediaderm TA Generics: Yes	0.5% Cream 0.1% Cream	-- --

*** italicized medications are branded products (reference listed drugs) that are not currently marketed.**

Appendix B—Corticosteroid Immune Modulators (Topical Steroids) Drugs in the Class (For UF decision see Appendix H)

Generic	Brand Generic	Strengths & formulations	Patent Exp
Low Potency Steroids (Class 6 and 7)			
Alclometosone dipropionate	Aclovate Generics: Yes	0.05% Cream, Ointment	--
Desonide	Desonate Desowen Verdeso Generics: Yes	0.05% Gel 0.05% Cream 0.05% Foam	08/2020 -- 09/2016
Fluocinolone acetonide	Capex Derma-Smoothe/FS Synalar Generics: Yes	0.01% Shampoo 0.01% Oil 0.01% Solution	-- -- --
Hydrocortisone	Ala-Cort Ala-Scalp Nutracort, Stie-Cort Synacort Texacort Pediaderm HC Generics: Yes	1% Lotion, Cream 2% Lotion 1%, 2.5% Lotion 1%, 2% Cream 2.5% Solution 2% Lotion + Emollient	-- -- -- -- -- --
Hydrocortisone acetate	Microcort Carmol HC, U-Cort Pramosone Epifoam Generics: Yes	2%, 2.5% Cream 1% Cream + 10% Urea 0.5%, 1% Cream + 1% Pramoxine 1%, 2.5% Lotion + 1% Pramoxine 1% Aerosol +1% Pramoxine	-- -- -- -- --

Appendix C—Self-Monitoring Blood Glucose System Test Strips Products in the Class

FREESTYLE LITE (ABBOTT)	ACCU-CHEK AVIVA
FREESTYLE INSULINX (ABBOTT)	ACCU-CHEK COMFORT CURVE
PRECISION XTRA (ABBOTT)	ACCU-CHEK SMARTVIEW
ACCU-CHEK AVIVA PLUS (ROCHE)	ACCUTREND GLUCOSE
GLUCOCARD 01-SENSOR (ARKRAY)	ACURA TEST STRIPS
GLUCOCARD (ARKRAY)	ADVANCE TEST STRIPS
CONTOUR NEXT (BAYER)	ADVOCATE REDI-CODE
NOVAMAX (NOVA)	ADVOCATE REDI-CODE+
TRUETEST (NIPRO DIAGNOSTICS)	ADVOCATE TEST STRIP
PRODIGY NO CODING (PRODIGY)	ASSURE 4
ACCU-CHEK	BG-STAR
ACCU-CHEK ACTIVE	BLOOD GLUCOSE TEST
ACCU-CHEK ADVANTAGE	CLEVER CHECK
ACCU-CHEK INSTANT	CLEVER CHOICE PRO
ASCENSIA ELITE	CONTOUR
ASSURE 3	CONTROL
ASSURE PLATINUM	EASY TOUCH
ASSURE PRO	EASYGLUCO
BD TEST STRIPS	EMBRACE
CHEMSTRIP BG	GE100 BLOOD GLUCOSE TEST STRIP
CLEVER CHOICE TEST STRIPS	GLUCOCARD EXPRESSION
DEXTROSTIX REAGENT	GLUCOCARD X SENSOR
EASY PRO PLUS	GLUCOLAB
EASYMAX	INFINITY
ELEMENT TEST STRIPS	INFINITY TEST STRIPS
EVENCARE G2	KEYNOTE
EZ SMART	LIBERTY TEST STRIPS
EZ SMART PLUS	MICRO
FAST TAKE	ONE TOUCH ULTRA
FIFTY50 TEST STRIP	ONE TOUCH VERIO
FORA G20	OPTIUM
FORA TEST STRIP	POCKETCHEM EZ
FORA V10	PRECISION PCX PLUS
FORA V30A	PRECISION Q-I-D
GLUCOMETER ENCORE	RELION CONFIRM MICRO
GLUCOSE TEST STRIP	RELION PRIME
GLUCOSTIX	RIGHTEST GS300 TEST STRIPS
MICRODOT	SMARTDIABETES XPRES
OPTIUM EZ	SOLUS V2 TEST STRIPS
PRECISION PCX	SURESTEP
PRECISION POINT OF CARE	TELCARE
PRESTIGE SMART SYSTEM	TEST STRIP
PRESTIGE TEST	TRUE TRACK
PRODIGY	TRUETRACK SMART SYSTEM
RIGHTEST GS100 TEST STRIPS	ULTIMA
RIGHTEST GS550 TEST STRIPS	ULTRATRAK
SMARTEST TEST	ULTRATRAK PRO
SURECHEK TEST STRIPS	VICTORY
SURESTEP PRO	WAVESENSE AMP
TRACER BG	WAVESENSE JAZZ
	WAVESENSE PRESTO

Appendix D—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Amcinonide 0.1% ointment (Cyclocort, generics) • Diflorasone 0.05% cream and ointment (Apexicon, generics) • Fluocinonide 0.1% cream (Vanos) • Halcinonide 0.1% cream and ointment (Halog) **High Potency Topical Steroids**	• Use of the formulary agent is contraindicated • All other formulary agents have resulted in therapeutic failure. Formulary alternatives include the high potency topical steroids - clobetasol, augmented betamethasone dipropionate, desoximetasone, fluocinonide 0.05%, halobetasol propionate.
• Amcinonide 0.1% cream and lotion (Cyclocort, generics) • Betamethasone valerate 0.12% foam (Luxiq, generics) • Clocortolone 0.1% cream (Cloderm) • Desonide 0.05% lotion (Desowen, generics) • Hydrocortisone probutate 0.1% cream (Pandel) • Hydrocortisone butyrate 0.1% cream and lotion (Locoid) • Triamcinolone with emollient #45, 0.1% cream kit (Pediaderm TA) **Medium Potency Topical Steroids**	• Use of all other medium potency formulary agents is contraindicated, and using a high potency agent would incur unacceptable risk. • All other Mid Potency formulary agents have resulted in therapeutic failure and using a High Potency agent would incur unacceptable risk. • For clocortolone, the patient requires a Coopman Class C agent, and desoximetasone is contraindicated. Formulary alternatives include the high potency and medium potency topical steroids
• Desonide 0.05% foam (Verdeso) • Desoinde 0.05 gel (Desonate) • Fluocinolone 0.01% shampoo (Capex) • Hydrocortisone with emollient #45, 2% lotion kit (Pediaderm HC) **Low Potency Topical Steroids**	• Use of all other low potency formulary agents, including over-the-counter topical steroids are contraindicated and using a higher potency agent would incur unacceptable risk. • All other low potency formulary topical steroids have resulted in therapeutic failure and using a higher potency agent would incur unacceptable risk. • For Desonide 0.05% foam (Verdeso) and fluocinolone 0.01% shampoo (Capex), requires a trial of fluocinolone oil (Derma-Smoothe/FS) unless patient has a contraindication specifically to Derma-Smoothe/FS Formulary alternatives include high, medium, and low potency topical steroids
• ACCU-CHEL Aviva Plus (Roche) • GLUCOCARD 01-Sensor (Arkray) • GLUCOCARD Vital (Arkray) • CONTOUR NEXT (Bayer) • NovaMAx (Nova) • TRUEtest (Nipro Diagnostics) • Prodigy No Coding (Prodigy) • One Touch Ultra (Lifescan) • One Touch Verio (Lifescan) • All other test strips listed in Appendix C with the exception of FreeStyle Lite, FreeStyle InsuLinx, and Precision Xtra **SMBG System Test Strips**	• No alternative formulary agent. o Patient is blind/severely visually impaired and requires a test strip used in a talking meter - Prodigy Voice, Prodigy AutoCode, Advocate Redicode. o Patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter. o The patient has a documented physical or mental health disability requiring a special strip meter. o Provider is concerned about the glucose dehydrogenase-pyrroloquinolinequinone interaction (GDH-PQQ) and the patient is taking IVIG Octagam.

Appendix E—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• ACCU-CHEK Aviva Plus (Roche) • GLUCOCARD 01-Sensor (Arkray) • GLUCOCARD Vital (Arkray) • CONTOUR NEXT (Bayer) • NovaMax (Nova) • TRUEtest (Nipro Diagnostics) • Prodigy No Coding (Prodigy) • One Touch Ultra (Lifescan) • One Touch Verio (Lifescan) • All other SMBG test strips listed in Appendix C, with the exception of FreeStyle Lite, FreeStyle InsuLinx, and Precision Xtra **Self-Monitoring Blood Glucose (SMBG) Test Strips**	New and current users of the nonformulary test strips are required to try FreeStyle Lite, FreeStyle InsuLinx, or Precision Xtra Manual PA Criteria—Non-Preferred test strip allowed if: • Patient is blind/severely visually impaired and requires a test strip used in a talking meter - Prodigy Voice, Prodigy AutoCode, Advocate Redicode • Patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter o Contour NEXT strip with CONTOUR NEXT Link meter for Medtronic pump o NovaMax strip with NovaMax Link meter for Medtronic pump o OneTouch Ultra test strips with One Touch Ultra Link meter for Medtronic Mini Med Paradigm insulin pump o OneTouch Ultra test strips with One Touch Ping meter and using the One Touch Ping insulin pump • The patient has a documented physical or mental health disability requiring a special strip or meter. • The patient is receiving peritoneal dialysis or the intravenous immune globulin (IVIG) preparation Octagam and the provider is concerned about the glucose dehydrogenase-pyrroloquinolinequinone interaction (GDH-PQQ)
• Injectable Corticotropin (HP Acthar Gel)	All new and current users of HP Acthar Gel are required to undergo Prior Authorization. Manual PA Criteria • Coverage is approved for infantile spasms (West Syndrome) in the following patients: Patient is less than 24 months old at initiation of treatment, and has no previous treatment with corticotrophin. Prior Authorization will expire in 30 days. Retreatment is not covered. • Coverage for acute exacerbations of multiple sclerosis and/or optic neuritis, acute gout and protein-wasting nephropathies—may be permitted on appeal. Prior Authorization will expire in 21 days for multiple sclerosis; 14 days for acute gout; and 6 months for protein-wasting nephropathies. • Coverage is not provided for the following uses: dermatomyositis, polymyositis, psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis and ankylosing spondylitis), sarcoidosis, serum sickness, Stevens-Johnson Syndrome (severe erythema multiforme), and systemic lupus erythematosis

Drug / Drug Class	Prior Authorization Criteria
• pyridoxine/doxylamine (Diclegis) **Antiemetics**	All new users of Diclegis are required to try a nonpharmacologic method for management of nausea and vomiting during pregnancy AND OTC pyridoxine before receiving pyridoxine/doxylamine (Diclegis). Manual PA criteria—Pyridoxine/doxylamine (Diclegis) is approved if: • The patient has not had relief of symptoms after trying a nonpharmacologic method to manage nausea and vomiting during pregnancy, AND • The patient has not had relief of symptoms after trying OTC pyridoxine for management of nausea and vomiting during pregnancy • Providers are encouraged to consider an alternate antiemetic (e.g., ondansetron) prior to prescribing pyrodixone/doxylamine. Prior Authorization will expire after 9 months.
• Ustekinumab (Stelara) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with • Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy No expiration date for Prior Authorization
• Golimumab (Simponi) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with • Moderate to severely active rheumatoid arthritis and active psoriatic arthritis, active ankylosing spondylitis • **Moderate to severely active ulcerative colitis that has not responded to other treatments or who require continuous steroids** • Coverage NOT provided for concomitant use with other TIBs, Kineret, Enbrel, Remicade, Orencia, or Rituxan No expiration date for Prior Authorization

Appendix F—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
Self-Monitoring Blood Glucose Test Strips (all products)	▪ Retail: 150 strips/30-day supply ▪ Mail Order and MTF: 450 strips/90-day supply
• Ustekinumab (Stelara) **Targeted Immunomodulatory Biologics (TIBs)**	▪ Retail: 2 pre-filled syringes (45 mg/0.5 mL; 90 mg/1.0 mL) or 2 vials (45 mg; 90 mg) /30 days ▪ Mail: 2 pre-filled syringes (45 mg/0.5 mL; 90 mg/1.0 mL) or 2 vials (45 mg; 90 mg) /56 days
• Golimumab (Simponi) **Targeted Immunomodulatory Biologics (TIBs)**	▪ Retail: 3 syringes (3 mL) /30 days ▪ Mail: 4 syringes (4mL) /56 days
• Dabrafenib (Tafinlar) **Oral chemotherapy drug**	50 mg and 75 mg capsules ▪ Retail: 120 capsules/30 days ▪ Mail Order: 240 capsules/60 days
• Trametinib (Mekinist) **Oral chemotherapy drug**	2 mg tablets ▪ Retail: 30 tablets/30 days ▪ Mail Order: 60 tablets/60 days 0.5 mg ▪ Retail: 120 tablets/30 days ▪ Mail Order 240 tablets/60 days
• Afatinib (Giotrif) **Oral chemotherapy drug**	40mg, 30mg, 20mg tablets ▪ Retail: 30 tablets/30 days ▪ Mail Order: 60 tablets/60 days

Appendix G—Drugs Designated as NF due to Section 703

Manufacturer	Drugs
Bausch & Lomb Rx	Besivance ophthalmic suspension
Fougera	methscopolamine tablets
Graceway Pharma	Zyclara cream
Kedrion	Gammaked injection
Meda Pharma	Dymista nasal spray
Neurogesx, Inc	Qutenza patch
Novartis Consumer	Transderm Scop
Otsuka America	Pletal
Patriot Pharma	Haldol injection; Itraconazole tabs/caps; Ketoconazole Shampoo; Galantamine Tabs; Tramadol ER Tabs
Pharmaderm	Oxistat products; Cutivate lotion; Temovate products
Rhodes Pharm	Hydromorphone; Tramadol ER
Sandoz	Calcitonin Nasal Spray; Calcium Acetate; Carbamazepine XR; Lansoprazole; Losartan; Losartan/HCTZ; Oxcarbazepine Susp; Sumatriptan Nasal Spray; Valsartan/HCTZ; Metoprolol/HCTZ; Rivastigmine
Stiefel Labs	Veltin
United Research Lab	Glycopyrrolate Tabs; Nisoldipine ER
Viropharma Inc	Vancocin Caps

See p 10. Patriot Pharmaceuticals has now signed a pricing agreement for all of its covered drugs. Qutenza patch and Zyclara cream are excluded from this action.

Appendix H—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2013	**Topical Steroids**	UF Class Review	▪ clobetasol 0.05% cream and ointment ▪ fluocinonide 0.05% cream and ointment ▪ triamcinolone acetate 0.1% cream and ointment	▪ aclometasone 0.05% cream, ointment (Aclovate, generics) ▪ augmented betamethasone dipropionate 0.05% cream, ointment, gel & lotion (Diprolene, Diprolene AF, generics) ▪ betamethasone dipropionate 0.05% cream & lotion (Diprosone, generics) ▪ betamethasone valerate 0.1% cream, ointment & lotion (Valisone, generics) ▪ clobetasol 0.05% solution, foam, gel, shampoo, lotion & spray (Clobex, Olux, Temovate, generics) ▪ desonide 0.05% cream & ointment (Desowen, generics) ▪ desoximetasone 0.05% & 0.25% cream, ointment, gel, & spray (Topicort, generics) ▪ fluocinonide 0.05%, gel, and solution (Lidex, generics) ▪ fluocinolone acetonide 0.01% oil, solution (Derma-Smoothe/FS, generics) ▪ fluocinolone 0.025% cream & ointment (Synalar, generics) ▪ flurandrenolide 4mcg/sq cm tape (Cordran) ▪ flurandrenolide 0.05% cream, lotion (Cordran, generics) ▪ fluticasone 0.005% ointment, & 0.05% cream & lotion (Cutivate, generics)	**High potency** ▪ mcinonide 0.1% ointment (Cyclocort, generics) ▪ iflorasone 0.05% cream & ointment (Apexicon, generics) ▪ luocinonide 0.1% cream (Vanos) ▪ alcinonide 0.1% cream & ointment (Halog) **Medium potency** ▪ mcinonide 0.1% cream & lotion (Cyclocort, generics) ▪ etamethasone valerate 0.12% foam (Luxiq, generics) ▪ locortolone 0.1% cream (Cloderm) ▪ esonide 0.05% lotion (Desowen, generics) ▪ hydrocortisone probutate 0.1% cream (Pandel) ▪ ydrocortisone butyrate 0.1% cream & lotion (Locoid) ▪	Pending signing of the minutes/ 60 days	N/A	-

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have onformulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
				▪ halobetasol 0.05% cream, ointment, lotion foam, & combinations (Halonate, Ultravate, generics) ▪ hydrocortisone 1%, 2% &2.5% cream, solution & lotion (excludes Pediaderm HC) ▪ hydrocortisone acetate 2% & 2.5% cream (Microcort-HC) generics ▪ hydrocortisone butyrate 0.1% ointment & solution (Locoid) ▪ hydrocortisone valerate 0.2% cream and ointment (Westcort, generics) ▪ mometasone 0.1% cream, ointment & solution (Elocon, generics) ▪ prednicarbate 0.1% cream & ointment (Dermatop, generics) ▪ triamcinolone acetate 0.025%, 0.05%, 0.1%, & 0.5% cream, ointment & lotion (excludes Pediaderm TA) ▪ triamcinolone acetate 0.015% spray (Kenalog) ▪ triamcinolone acetonide 0.5% cream (Artistocort A, generics)	riamcinolone acetonide with emollient #45, 0.1% cream kit (Pediaderm TA) **Low potency** ▪ esonide 0.05% foam (Verdeso) & 0.05% gel (Desonate) ▪ luocinolone 0.01% shampoo (Capex) **Low potency (continued)** ▪ ydrocortisone with emollient #45, 2% lotion kit (Pediaderm HC)			

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2013	**Self-Monitoring Blood Glucose System (SMBS) test strips**	UF Class Review	▪ FreeStyle Lite (Abbott)	Uniform Formulary and Step-Preferred ▪ FreeStyle Lite (Abbott) ▪ FreeStyle InsuLinx (Abbott) ▪ Precision Xtra (Abbott)	Nonformulary and non-step preferred ▪ACCU-CHEK Aviva Plus (Roche) ▪GLUCOCARD 01-SENSOR (Arkray) ▪GLUCOCARD (Arkray) ▪CONTOUR NEXT (Bayer) ▪NovaMax (Nova) ▪TRUEtest (Nipro) ▪Prodigy No Coding (Prodigy) ▪One Touch Ultra (Lifescan) ▪One Touch Verio (Lifescan) ▪All other test strips listed in Appendix C, with the exception of Freestyle Lite, Freestyle InsuLinx, and Precision Xtra	Pending signing of the minutes / 120 days	Step therapy requires a trial of an Abbott test strip (FreeStyle Lite, FreeStyle InsunLinx, or Precision Xtra) in all new and current users of the nonformulary strips	▪ FreeStyle Lite added to the BCF ▪ PrecisionXtra removed from the BCF, but still UF and step-preferred

Appendix I—Table of Abbreviations

ARBs	Angiotensin Receptor Blockers
ASD(HA)	Assistant Secretary of Defense for Health Affairs
BCF	Basic Core Formulary
BIA	budget impact analysis
BPH	benign prostatic hyperplasia
CMA	cost minimization analysis
DoD	Department of Defense
DRIs	Direct Renin Inhibitors
FDA	U.S. Food and Drug Administration
GDH-PQQ	glucose dehydrogenase-pyrroloquinolinequinone
ISO	International Organization for Standardization
LIP-1s	Antilipidemic-1s Drug Class
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
MCSCs	Managed Care Support Contractors
NF	nonformulary
NVP	nausea and vomiting in pregnancy
OTC	over-the-counter
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
SMBGS	Self-Monitoring Blood Glucose System (SMBGS)
TMA	TRICARE Management Activity
TIBs	targeted immunomodulatory biologics
UF	Uniform Formulary

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2013

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Non-Insulin Diabetes Drugs: Sodium Glucose Co-Transporter 2 (SGLT2)Inhibitors—Canagliflozin (Invokana)

Relative Clinical Effectiveness Conclusion—Canagliflozin (Invokana) is a new diabetes drug with a novel mechanism of action and the first FDA-approved SGLT2 inhibitor. SGLT2 inhibitors are a new subclass of the Non-Insulin Diabetes Drug Class. The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee concluded (15 for, 1 opposed, 0 abstained, 1 absent) that despite its unique mechanism of action to increase urinary glucose excretion, canagliflozin (Invokana) does not offer a clinically compelling advantage over the other non-insulin drugs included on the Uniform Formulary (UF). Canagliflozin has several safety concerns in the setting of modest decreases in hemoglobin A1c.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that canagliflozin (Invokana) is not cost-effective compared to other non-insulin diabetes drugs currently available on the UF. Cost minimization analysis (CMA) showed canagliflozin is more costly than metformin, glyburide, pioglitazone (Actos, generic), sitagliptin (Januvia), and exenatide (Byetta), in terms of cost per day of therapy.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) canagliflozin (Invokana) be designated nonformulary (NF) due to the lack of compelling clinical advantages, safety concerns, lack of long-term outcomes and adverse event data, and cost disadvantage compared to UF products.

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) the following MN criteria for canagliflozin (Invokana): use of formulary agents is contraindicated. (See Appendix B for full criteria.)

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
In the Non-Insulin Diabetes Drug Class, existing automated prior authorization (step therapy) requires a trial of metformin or a sulfonylurea, prior to the use of a dipeptidyl-dipeptidase-4 (DPP-4) inhibitor, a thiazolidinedione (TZD), or a glucagon-like peptide-1 receptor agonist (GLP1RA), based on positive efficacy and long-term outcomes data with metformin and the sulfonylureas.

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) a trial of metformin, a sulfonylurea, or a DPP-4 inhibitor in all new and current users of SGLT2 inhibitors, canagliflozin (Invokana), due to the modest hemoglobin A1c lowering and safety concerns. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is September 11, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

II. UF DRUG CLASS REVIEWS

A. Anti-Gout Drugs

Relative Clinical Effectiveness Conclusion—The P&T Committee evaluated the Anti-Gout Drug Class. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions:

- Colchicine is a very old drug that is available in one branded formulation, (Colcrys), which has a patent extending to 2029.
- For an acute gout attack, clinical practice guidelines support colchicine as first line treatment, along with non-steroidal anti-inflammatory drugs (NSAIDs) or prednisone. Treatment should be initiated within the first 24 hours of symptom onset.

- For chronic gout, urate lowering therapy (ULT) with allopurinol or febuxostat is recommended as first line. Based on head-to-head trials, febuxostat (Uloric) 40 mg and allopurinol 300 mg were equally efficacious in lowering serum uric acid (sUA) to less than 6mg/dL in one study (CONFIRMS). Febuxostat 80 mg was superior to allopurinol 300 mg in lowering sUA to less than 6mg/dL in two studies (FACT and APEX).
- Higher doses of allopurinol (doses > 300mg), although not well studied, may be required in some patients to decrease sUA.
- Systematic reviews from the Cochrane group, and evidence-based organizations from Canada, the United Kingdom, and Europe recommend febuxostat as an alternative ULT in patients who cannot tolerate allopurinol.
- In terms of clinical coverage, one anti-inflammatory agent (colchicine) and one xanthine oxidase inhibitor (allopurinol or febuxostat) is required on the UF to meet the needs of the majority of DoD beneficiaries.

Relative Cost-Effectiveness Conclusion—Pharmacoeconomic analyses were performed for the Anti-Gout Drug Class, including CMA and budget impact analysis (BIA). The class was subdivided into chronic drugs (allopurinol and febuxostat) and acute drugs (colchicine).

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) generic allopurinol (Zyloprim) was the most cost-effective of the chronic drugs, followed by branded febuxostat (Uloric), based on the weighted average cost per day of treatment across all three POS. Branded colchicine (Colcrys) was the only acute agent examined in the analysis; a cost analysis was conducted. Results from the CMA and BIA showed that among available formulary options examined, scenarios where allopurinol (Zyloprim) is the Basic Core Formulary (BCF) step-preferred agent, febuxostat (Uloric) is the NF non-preferred agent (with all current and new users required to try allopurinol first), and colchicine (Colcrys) is UF presented a maximum cost-avoidance projection.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 4 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS:
    - allopurinol be designated UF and step-preferred (e.g., "in front of the step");
    - febuxostat (Uloric) be designated NF and non step-preferred (e.g., "behind the step"); and

- colchicine (Colcrys), probenecid, and the fixed dose combination of colchicine/probenecid be designated formulary on the UF and exempt from step therapy.
- This recommendation includes step therapy, which requires a trial of allopurinol prior to using febuxostat (Uloric) in all current and new users of febuxostat.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining allopurinol as BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for febuxostat (Uloric). (See Appendix B for full criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—After extensive discussion, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for all current and new users of febuxostat (Uloric), requiring a trial of allopurinol prior to use of febuxostat. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Additional recommendations made by the P&T Committee were to provide messaging to retail pharmacies to designate that PA and step therapy is required, with a trial of allopurinol prior to febuxostat (Uloric); and that the Anti-Gout Drug Class be added to the Rapid Response Program for the Retail Network and Mail Order Pharmacy. Based on the P&T Committee's recommendation, the effective date is November 6, 2013.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Pulmonary II Drugs

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following at the February 2013 meeting:

- Aclidinium inhaler (Tudorza) is the second long-acting muscarinic agent (LAMA) on the market. Three clinical trials reported statistically significant improvement in spirometric endpoints, and two of the trials reported significantly fewer chronic obstructive pulmonary disease (COPD) exacerbations, compared to placebo.
- For aclidinium, the adverse event profile appears minimal, with primarily anticholinergic events reported. Longer duration and larger comparative trials are needed to determine aclidinium's place in therapy.
- Several trials have shown the LAMA tiotropium (Spiriva) is associated with clinically significant improvements in spirometric endpoints and reductions in risk for COPD exacerbations. Tiotropium is also reported to reduce the proportion of patients hospitalized for COPD exacerbations.
- Reports of a possible link between tiotropium and adverse cardiovascular events including death, stroke, and myocardial infarction have not been confirmed in prospective trials.
- Roflumilast (Daliresp) is the first oral selective inhibitor of phosphodiesterase type 4 (PDE-4) marketed in the United States. In two clinical trials, roflumilast was associated with statistically significant reductions in the rate of COPD exacerbations.
- For roflumilast, safety issues identified by the FDA included psychiatric events (including suicide), weight loss, gastrointestinal upset and severe diarrhea, and nasal tumors. However, the FDA did not require additional prospective safety studies.
- Albuterol/ipratropium soft mist inhaler (Combivent Respimat) is the new propellant-free inhaler that is replacing the ozone-depleting chlorofluorocarbon (CFC)-containing Combivent metered dose inhaler (MDI). The clinical trial used to obtain FDA approval showed Combivent Respimat was non-inferior to Combivent CFC MDI in terms of improvements in spirometric endpoints.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) the following:

- CMA within the LAMA subclass showed that tiotropium (Spiriva) was more cost-effective than aclidinium (Tudorza). BIA results where Spiriva was designated BCF and Tudorza designated UF resulted in the greatest cost-avoidance to the MHS.

- CMA was conducted within the COPD subclass, which includes the short-acting muscarinic agents (SAMA), short-acting beta agonist (SABA)/SAMA combination drugs, and PDE-4 inhibitors. The results showed that ipratropium nebulized solution (Atrovent; generic) was the most cost-effective agent, followed by ipratropium/albuterol nebulized solution (DuoNeb; generic), ipratropium hydrofluoroalkane MDI (Atrovent HFA), ipratropium/albuterol soft mist inhaler (Combivent Respimat), and roflumilast (Daliresp). Ipratropium/albuterol (Combivent) was not included in the cost-effectiveness analysis due to market discontinuation by December 2013. BIA projections for all scenarios were very similar.

    1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 1 opposed, 2 abstained, 2 absent) aclidinium inhaler (Tudorza), tiotropium inhaler (Spiriva), ipratropium nebulized solution (Atrovent; generic), ipratropium/albuterol nebulized solution (DuoNeb; generic), ipratropium HFA MDI (Atrovent HFA), ipratropium/albuterol soft mist inhaler (Combivent Respimat), and roflumilast (Daliresp) remain designated Uniform Formulary. Ipratropium/albuterol MDI (Combivent) will remain designated UF, pending discontinuation in December 2013.

    2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (13 for, 0 opposed, 2 abstained, 2 absent) maintaining ipratropium HFA MDI (Atrovent HFA) and ipratropium/albuterol nebulized solution (DuoNeb; generic), on the BCF, and recommended adding tiotropium (Spiriva) to the BCF, upon signing of the minutes.

Director, TMA, Decision: ☒Approved □ Disapproved

Approved, but modified as follows:

C. Self-Monitoring Blood Glucose System (SMBGS) Test Strips

Background and Relative Clinical Effectiveness—The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips, including the attributes of the test strips and glucometers. Candidates for inclusion on the UF must meet all minimum required technical standards and United States Federal Government contracting requirements.

The P&T Committee reviewed the existing technical requirements approved in May 2007, and recommended updates to the criteria.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following for the minimum technical requirements and U.S. Federal Government contracting requirements for the SMBGS test strips. The full clinical effectiveness conclusion will be presented at the August 2013 meeting:

- *U.S Federal Government contracting requirements*: SMBGS test strips eligible for inclusion on the Uniform Formulary must be available at all 3 POS and must be compliant with the Trade Agreements Act. Corresponding SMBGS glucometers must also be compliant with the Trade Agreements Act. Manufacturers of SMBGS glucometers will be required to provide DoD beneficiaries with a no-cost glucometer.
- *Minimum technical requirements*: Candidate SMBGS test strips eligible for inclusion on the Uniform Formulary must meet minimum technical requirements in the areas of accuracy, sample size, alternate site testing, results time, memory capacity, ease of use, customer support, downloading capabilities, and data management capabilities. See pages 19-20 for detailed technical requirements.

Relative Cost-Effectiveness Conclusion—The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

D. Corticosteroid Immune Modulators (Topical Steroids)

The P&T Committee evaluated the Corticosteroid Immune Modulators (Topical Steroids) Drug Class. The class is comprised of 22 individual chemical entities, available in over 100 different formulations and vehicles. The Stoughton-Cornell classification system, which divides the drugs into seven classes based on their vasoconstrictive properties, was used to further divide the drugs into high- (classes 1 and 2 steroids), medium- (classes 3, 4, and 5), and low-potency agents (classes 6 and 7). Over-the-counter (OTC) products are excluded from the class.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 1 absent) with the clinical effectiveness conclusion. The full clinical effectiveness evaluation will be reported in the August meeting minutes.

Relative Cost-Effectiveness Conclusion—The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

III. BCF ISSUES

A. Emergency Contraceptives

The Emergency Contraceptives were last reviewed by the P&T Committee in August 2011. Levonorgestrel 0.75 mg (Next Choice, the generic for Plan B) was designated as BCF. Next Choice was discontinued by the manufacturer in early 2013. The currently available emergency contraceptives include levonorgestrel 0.75 mg available from a generic manufacturer; levonorgestrel 1.5 mg (Next Choice One Dose, Plan B One Step); and ulipristal (Ella). A prescription is required for all ages for Ella; and for patients under age 17 for generic levonorgestrel 0.75 mg, and levonorgestrel 1.5 mg (Next Choice One Dose). On April 15, 2013, the age restriction was lowered to under age 15 for Plan B One Step by the FDA. A cost analysis showed that Plan B One Step has the lowest cost of the currently available emergency contraceptives.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) upon signing of the minutes, to:
   a) remove levonorgestrel 0.75 mg (Next Choice) from the BCF; and
   b) add levonorgestrel 1.5 mg (Plan B One Step) to the BCF.
   c) No other changes to the Uniform Formulary are recommended; generic levonorgestrel 0.75 mg, levonorgestrel 1.5 mg (Next Choice One Dose, generic Plan B One Step), and ulipristal (Ella) remain UF.

2. ***COMMITTEE ACTION: QLs AND AGE LIMITS***—The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) upon signing of the minutes, to:
   a) maintain the current QLs at all three POS of one fill per prescription, with no refills (new prescription required for every fill).
   b) For the current age limits, MTFs should follow their individual service policies, and for the Mail Order and Retail points of service, the FDA labeling should be followed.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

As the FDA has now approved emergency contraceptive Plan B One-Step to be available over the counter without restrictions, and as regulations required by section 702 of the FY13 NDAA to include OTCs on the uniform formulary have not yet been

prescribed, no emergency contraceptive shall be included on the BCF. Nevertheless, MTFs shall ~~treat~~ carry Plan B One-Step as ~~any other OTC in deciding whether to~~ provide it, and at no cost.

B. Gastrointestinal-1 (GI-1) Drug Class—Mesalamine (Asacol)

The GI-1 Drug Class was previously reviewed by the P&T Committee in February 2011. Mesalamine delayed release tablets (Asacol) were designated as BCF. In March 2013, Asacol tablets were discontinued by the manufacturer, Warner Chilcott, and supplies have been depleted. Warner Chilcott subsequently received FDA approval for a new formulation, Delzicol capsules, which is substantially more costly than Asacol. Several other mesalamine delayed release tablets are on the UF, including Asacol HD, Apriso, Lialda, and Pentasa. These products use different proprietary methods to delay release of the drug into the large intestine and, therefore, are not interchangeable and have different FDA-approved indications and dosing.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) upon signing of the minutes, to:
   a) remove mesalamine delayed release tablets (Asacol) from the BCF.
   b) The GI-1 Drug Class will not have a designated BCF product until the class can be re-reviewed for UF status. MTFs are advised to order what they need to meet local needs.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UTILIZATION MANAGEMENT

A. PA

1. **Injectable Gonadotropins**—The P&T Committee clarified the PA criteria to set a 60-day expiration date for the PA, to help ensure that an authorization memorandum is included with each assisted reproductive technology (ART) cycle. A 60-day expiration is sufficient for a patient to complete an ART cycle.

   a) ***COMMITTEE ACTION: INJECTABLE GONADOTROPINS***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) clarifying the existing PA criteria for the injectable gonadotropins to have a 60-day expiration date for the PA.

2. **Proton Pump Inhibitors: Pantoprazole Change from Non-Preferred to Step-Preferred Status**—In November 2012, the P&T Committee recommended reclassification of pantoprazole as formulary on the UF, due to availability of cost-effective generic formulations; pantoprazole remained non-preferred. The cost of generic pantoprazole tablets has continued to decline since November 2012. The P&T Committee recommended revising the PA criteria to designate pantoprazole as step preferred (i.e., in front of the step).

    a) ***COMMITTEE ACTION: PANTOPRAZOLE PA CRITERIA/ STEP-PREFERRED STATUS***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) designating pantoprazole as step-preferred (i.e., in front of the step) on the UF.

3. **Antilipidemics-2: Icosapent ethyl (Vascepa)**—Icosapent ethyl (Vascepa) is the second prescription fish oil product marketed. The P&T Committee recommended manual PA criteria for all current and new users of Vascepa, limiting use to the FDA-approved indication; the manual PA criteria for Vascepa will be the same as criteria for Lovaza.

    a) ***COMMITTEE ACTION: ICOSAPENT ETHYL (VASCEPA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) manual PA criteria for all current and new users of Vascepa, limiting use to the FDA-approved indication. (See Appendix C for full criteria.)

4. **Abiraterone (Zytiga)**—PA criteria for abiraterone (Zytiga) were recommended at the November 2012 meeting, consistent with the FDA labeling. The FDA has subsequently updated the approved labeling for patients with metastatic castration-resistant prostate cancer with concomitant prednisone.

    a) ***COMMITTEE ACTION: ABIRATERONE (ZYTIGA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the abiraterone (Zytiga) PA criteria for use in patients with a documented diagnosis of metastatic castration-resistant prostate cancer on concomitant prednisone. The previous criterion for prior chemotherapy containing docetaxel is no longer required.

B. Quantity Limits (QLs)

1. **Oral tretinoin 10 mg capsules (Vesanoid)**—Oral tretinoin 10 mg capsules are approved for inducing remission in acute promyelocytic leukemia. Quantity limits are in place for several oral chemotherapy agents. The P&T Committee recommended QLs for oral tretinoin 10 mg capsules due to the high cost and adverse event profile.

   a) ***COMMITTEE ACTION: ORAL TRETINOIN 10MG CAPSULES (VESANOID) QLs***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) QLs/days supply limits for oral tretinoin 10 mg capsules (Vesanoid), based on FDA-approved labeling, limiting use to a 30-day supply in the Retail Network, and a 45-day supply in the Mail Order.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

8/6/2013
Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

May 2013

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 15, 2013, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of February 2013 Minutes**—Jonathon Woodson, M.D., Director, approved the minutes for the February 2013 DoD P&T Committee meeting on May 13, 2013.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Non-Insulin Diabetes Drugs: Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors—Canagliflozin (Invokana)

Relative Clinical Effectiveness Conclusion—Canagliflozin (Invokana) is a new diabetes drug with a novel mechanism of action and the first FDA-approved SGLT2 inhibitor. SGLT2 inhibitors are a new subclass of the Non-Insulin Diabetes Drug Class, which was originally reviewed in November 2010. The Non-Insulin Diabetes Drug Class also includes the following subclasses: biguanides (metformin), sulfonylureas,

thiazolidinedione (TZD), dipeptidyl-dipeptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP1RAs), pramlintide, dopamine agonists, meglitinides, and alpha glucosidase inhibitors.

The P&T Committee concluded (15 for, 1 opposed, 0 abstained, 1 absent):

- Efficacy of canagliflozin is limited to eight clinical trials, showing moderate decreases in hemoglobin A1c from baseline ranging from 0.63% (with insulin) to 1.11% (monotherapy in treatment-naïve patients).
- Canagliflozin has safety concerns of hypotension, impaired renal function, hyperkalemia, hypermagnesemia, hyperphosphatemia, increases in low-density lipoprotein (LDL) cholesterol and hemoglobin, hypoglycemia, urinary tract infections in both men and women, and genital mycotic infections.
- There is limited safety information available and no long-term outcomes trials have been completed to date with canagliflozin.
- Despite its unique mechanism of action to increase urinary glucose excretion, canagliflozin (Invokana) does not offer a clinically compelling advantage over the other non-insulin drugs included on the UF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that canagliflozin (Invokana) is not cost-effective compared to other non-insulin diabetes drugs currently available on the UF. Cost minimization analysis (CMA) showed canagliflozin is more costly than metformin, glyburide, pioglitazone (Actos, generic), sitagliptin (Januvia), and exenatide (Byetta), in terms of cost per day of therapy.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) canagliflozin (Invokana) be designated NF due to the lack of compelling clinical advantages, safety concerns, lack of long-term outcomes and adverse event data, and cost disadvantage compared to UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) the following MN criteria for canagliflozin (Invokana): use of formulary agents is contraindicated. (See Appendix B for full criteria.)

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—In the Non-Insulin Diabetes Drug Class, existing automated prior authorization (step therapy) requires a trial of metformin or a

sulfonylurea, prior to the use of a DPP-4 inhibitor, a TZD, or a GLP1RA, based on positive efficacy and long-term outcomes data with metformin and the sulfonylureas.

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) a trial of metformin, a sulfonylurea, or a DPP-4 inhibitor in all new and current users of SGLT2 inhibitors, canagliflozin (Invokana), due to the modest hemoglobin A1c lowering and safety concerns. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is September 11, 2013.

V. UF DRUG CLASS REVIEWS

A. Anti-Gout Drugs

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the Anti-Gout Drug Class. This class has not been previously reviewed for UF placement. Drugs in the class include allopurinol (Zyloprim, generic), probenecid, colchicine (Colcrys), colchicine/probenecid, and febuxostat (Uloric). Allopurinol is currently designated as a BCF product (pre-UF Rule decision).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions:

- Colchicine is a very old drug that is available in one branded formulation, (Colcrys), which has a patent extending to 2029.
- For an acute gout attack, clinical practice guidelines support colchicine as first line treatment, along with non-steroidal anti-inflammatory agents (NSAIDs) or prednisone. Treatment should be initiated within the first 24 hours of symptom onset.
- For chronic gout, urate-lowering therapy (ULT) with allopurinol or febuxostat is recommended as first line. Based on head-to-head trials, febuxostat (Uloric) 40 mg and allopurinol 300 mg were equally efficacious in lowering serum uric acid (sUA) to less than 6mg/dL in one study

(CONFIRMS). Febuxostat 80 mg was superior to allopurinol 300 mg in lowering sUA to less than 6mg/dL in two studies (FACT and APEX).

- Higher doses of allopurinol (doses > 300mg), although not well studied, may be required in some patients to decrease sUA.
- Systematic reviews from the Cochrane group, and evidence-based organizations from Canada, the UK, and Europe recommend febuxostat as an alternative ULT in patients who cannot tolerate allopurinol.
- Use of colchicine for prophylaxis helps prevent gout flares during initiation of ULT. However, in published trials, gout flares increased when prophylaxis was discontinued. Guidelines recommend administering colchicine or NSAID prophylaxis for up to 6 months.
- Head-to-head studies show similar rates of adverse events with febuxostat and allopurinol.
- Febuxostat warnings from the FDA include liver enzyme elevations. Liver function tests should be tested at initiation of therapy and monitored throughout treatment.
- Febuxostat warnings from the European Medicines Association (EMA) include the potential for increased cardiovascular (CV) events. According to the EMA, febuxostat should not be used in patients with ischemic heart disease or congestive heart failure, due to increased risk of CV events.
- In terms of clinical coverage, one anti-inflammatory agent (colchicine) and one xanthine oxidase inhibitor (allopurinol or febuxostat) are required on the UF to meet the needs of the majority of DoD beneficiaries.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses were performed for the Anti-Gout Drug Class, including CMA and budget impact analyses (BIAs). The class was subdivided into chronic drugs (allopurinol and febuxostat) and acute drugs (colchicine). For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) generic allopurinol (Zyloprim) was the most cost-effective of the chronic drugs, followed by branded febuxostat (Uloric), based on the weighted average cost per day of treatment across all three POS. Branded colchicine (Colcrys) was the only acute agent examined in the analysis; a cost analysis was conducted. CMA and BIA results showed that among available formulary options examined, scenarios where allopurinol (Zyloprim) is the BCF step-preferred agent, febuxostat (Uloric) is the NF non-preferred agent (with all current and new users required to try allopurinol first), and colchicine (Colcrys) is UF presented a maximum cost-avoidance projection.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 4 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS:
    - allopurinol be designated UF and step-preferred (e.g., "in front of the step") ;
    - febuxostat (Uloric) be designated NF and non step-preferred (e.g., "behind the step"); and
    - colchicine (Colcrys), probenecid, and the fixed dose combination of colchicine/probenecid be designated formulary on the UF and exempt from step therapy.
    - This recommendation includes step therapy, which requires a trial of allopurinol prior to using febuxostat (Uloric) in all current and new users of febuxostat.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining allopurinol as BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for febuxostat (Uloric). (See Appendix B for full criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—After extensive discussion, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for all current and new users of febuxostat (Uloric), requiring a trial of allopurinol prior to use of febuxostat. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Additional recommendations made by the P&T Committee were to provide messaging to retail pharmacies to designate that PA and step therapy is required, with a trial of allopurinol prior to febuxostat (Uloric) and that the Anti-Gout Drug Class be added to the Rapid Response Program for the Retail Network and Mail Order Pharmacy. Based on the P&T Committee's recommendation, the effective date is November 6, 2013.

B. Pulmonary II Drugs

Background and Relative Clinical Effectiveness—The Pulmonary II Drug Class is comprised of two subclasses, the long-acting muscarinic agents (LAMAs), aclidinium inhaler (Tudorza) and tiotropium inhaler (Spiriva), and the chronic obstructive pulmonary disease (COPD) drugs [comprised of the short-acting muscarinic agents (SAMAs), short-acting beta agonist (SAMA/SABA) combinations and the phosphodiesterase type 4 (PDE-4) inhibitors].

Combivent metered dose inhaler (MDI) is one of the last available chlorofluorocarbon (CFC) MDIs on the market and will have supplies exhausted by December 2013. Its replacement is Combivent Respimat, a new CFC- and propellant-free formulation.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following at the February 2013 meeting:

- Aclidinium inhaler (Tudorza) is the second LAMA on the market. The three clinical trials used to obtain FDA approval reported statistically significant improvement in spirometric endpoints, and two of the trials reported significantly fewer COPD exacerbations with aclidinium, compared to placebo.
- For aclidinium, the adverse event profile appears minimal, with primarily anticholinergic events reported. However, there is limited safety data with the 400 mcg approved dose. The FDA requires a prospective clinical trial to assess CV safety. Longer duration and larger comparative trials are needed to determine aclidinium's place in therapy.
- Several trials have shown the LAMA tiotropium (Spiriva) is associated with clinically significant improvements in spirometric endpoints and reductions in risk for COPD exacerbations. Tiotropium is also reported to reduce the proportion of patients hospitalized for COPD exacerbations.
- Reports of a possible link between tiotropium and adverse CV events including death, stroke, and myocardial infarction have not been confirmed in prospective trials.
- Roflumilast (Daliresp) is the first oral selective inhibitor of PDE-4 marketed in the United States. Its FDA indication is limited to reducing the incidence of COPD exacerbations in patients with severe COPD. In two clinical trials, roflumilast was associated with statistically significant reductions in the rate of COPD exacerbations.
- For roflumilast, safety issues identified by the FDA included psychiatric events (including suicide), weight loss, gastrointestinal upset and severe diarrhea, and

nasal tumors. However, the FDA did not require additional prospective safety studies. A risk evaluation and mitigation strategy program was not required.

- Albuterol/ipratropium inhaler (Combivent Respimat) is the new propellant-free inhaler that is replacing the ozone-depleting CFC-containing Combivent MDI. The clinical trial used to obtain FDA approval showed Combivent Respimat was non-inferior to Combivent CFC MDI in terms of improvements in spirometric endpoints.

Relative Cost-Effectiveness Analysis and Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) the following:

- CMA within the LAMA subclass showed that tiotropium (Spiriva) was more cost-effective than aclidinium (Tudorza). BIA results where Spiriva was designated BCF and Tudorza designated UF resulted in the greatest cost-avoidance to the MHS.
- CMA was conducted within the COPD subclass, which includes the SAMAs, SABA/SAMA combination drugs, and PDE-4 inhibitors. The results showed ipratropium nebulized solution (Atrovent; generic) was the most cost-effective agent, followed by ipratropium/albuterol nebulized solution (DuoNeb; generic), ipratropium hydrofluoroalkane (HFA) MDI (Atrovent HFA), ipratropium/albuterol soft mist inhaler (Combivent Respimat), and roflumilast (Daliresp). Ipratropium/albuterol (Combivent) was not included in the cost-effectiveness analysis due to market discontinuation by December 2013. BIA projections for all scenarios were very similar.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 1 opposed, 2 abstained, 2 absent) aclidinium inhaler (Tudorza), tiotropium inhaler (Spiriva), ipratropium nebulized solution (Atrovent; generic), ipratropium/albuterol nebulized solution (DuoNeb; generic), ipratropium HFA MDI (Atrovent HFA), ipratropium/albuterol soft mist inhaler (Combivent Respimat), and roflumilast (Daliresp) remain designated UF. Ipratropium/albuterol MDI (Combivent) will remain designated UF, pending discontinuation in December 2013.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (13 for, 0 opposed, 2 abstained, 2 absent) maintaining ipratropium HFA MDI (Atrovent HFA) and ipratropium/albuterol nebulized solution (DuoNeb; generic) on the BCF, and recommended adding tiotropium (Spiriva) the BCF, upon signing of the minutes.

C. Self-Monitoring Blood Glucose System (SMBGS) Test Strips

Background and Relative Clinical Effectiveness—The P&T Committee reviewed the clinical effectiveness of the SMBGS test strips, including the attributes of the test strips and glucometers. The SMBGS test strips were previously reviewed for UF placement in August 2008. The primary goal for this review is to ensure uniform availability of quality SMBGS test strips across the MHS (MTF, Retail, and Mail Order points of service). SMBGS glucometers are not included as part of the TRICARE outpatient pharmacy benefit (they are included under the medical benefit) and are not the focus of the review; however, provisions have been made to provide SMBGS glucometers at no cost to MHS beneficiaries.

The FDA classifies SMBGS test strips and glucometers as medical devices, rather than drugs, thus the focus of the clinical effectiveness review centers on differences in the technical aspects/attributes among the products. Candidates for inclusion on the UF must meet all minimum required technical standards and United States Federal Government contracting requirements. The P&T Committee reviewed the existing technical requirements approved in May 2007, and recommended updates to the criteria.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following for the minimum technical requirements and U.S. Federal Government contracting requirements for the SMBGS test strips. The full clinical effectiveness conclusion will be presented at the August 2013 meeting:

- *U.S Federal Government contracting requirements*: SMBGS test strips eligible for inclusion on the Uniform Formulary must be available at all 3 POS and must be compliant with the Trade Agreements Act. Corresponding SMBGS glucometers must also be compliant with the Trade Agreements Act. Manufacturers of SMBGS glucometers will be required to provide DoD beneficiaries with a no-cost glucometer.
- *Minimum technical requirements*: Candidate SMBGS test strips eligible for inclusion on the Uniform Formulary must meet the following minimum technical requirements:
    - Accuracy: Must meet FDA standards for accuracy based on the International Organization for Standardization (ISO) 15197 guidelines.
    - Sample size of $\leq$ 1 microliter
    - Alternate site testing: more than one alternate site approved.
    - Result time: $\leq$ 10 seconds
    - Memory capacity: $\geq$ 250 readings

- Ease of use: glucometer must be easy to code/calibrate, have a large visual display, and be easy to handle for patients with dexterity issues.
- Customer support: 24-hour helpline available, for beneficiaries residing outside the continental United States.
- Downloading capabilities: results must be downloadable
- Data management capabilities: data management capabilities required (e.g., software, cloud computing).

Relative Cost-Effectiveness Conclusion—The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

D. Corticosteroid Immune Modulators (Topical Steroids)

The P&T Committee evaluated the Corticosteroid Immune Modulators (Topical Steroids) Drug Class. The class is comprised of 22 individual chemical entities, available in over 100 different formulations and vehicles. The Stoughton-Cornell classification system, which divides the drugs into seven classes based on their vasoconstrictive properties, was used to further divide the drugs into high- (classes 1 and 2 steroids), medium- (classes 3, 4, and 5), and low-potency agents (classes 6 and 7). Over-the-counter (OTC) products are excluded from the class.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 1 absent) with the clinical effectiveness conclusion. The full clinical effectiveness evaluation will be reported in the August meeting minutes.

Relative Cost-Effectiveness Conclusion—The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

VI. BCF ISSUES

A. Emergency Contraceptives

The Emergency Contraceptives were last reviewed by the P&T Committee in August 2011. Levonorgestrel 0.75 mg (Next Choice, the generic for Plan B) was designated as BCF. Next Choice was discontinued by the manufacturer in early 2013. The currently available emergency contraceptives include levonorgestrel 0.75 mg available from a

generic manufacturer; levonorgestrel 1.5 mg (Next Choice One Dose, Plan B One Step); and ulipristal (Ella). A prescription is required for all ages for Ella; and for patients under age 17 for generic levonorgestrel 0.75 mg, and levonorgestrel 1.5 mg (Next Choice One Dose). On April 15, 2013, the age restriction was lowered to under age 15 for Plan B One Step by the FDA. A cost analysis showed that Plan B One Step has the lowest cost of the currently available emergency contraceptives.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) upon signing of the minutes, to:
   a) remove levonorgestrel 0.75 mg (Next Choice) from the BCF; and
   b) add levonorgestrel 1.5 mg (Plan B One Step) to the BCF.
   c) No other changes to the Uniform Formulary are recommended; generic levonorgestrel 0.75 mg, levonorgestrel 1.5 mg (Next Choice One Dose, generic Plan B One Step), and ulipristal (Ella) remain UF.

2. ***COMMITTEE ACTION: QLs AND AGE LIMITS***—The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) upon signing of the minutes, to:
   a) maintain the current QLs at all three POS of one fill per prescription, with no refills (new prescription required for every fill).
   b) For the current age limits, MTFs should follow their individual service policies, and for the Mail Order and Retail points of service, the FDA labeling should be followed.

Note from Decision Paper on p 8: As the FDA has now approved emergency contraceptive Plan B One-Step to be available over the counter without restrictions, and as regulations required by section 702 of the FY13 NDAA to include OTCs on the uniform formulary have not yet been prescribed, no emergency contraceptive shall be included on the BCF. MTFs shall ~~treat~~ Plan B One-Step ~~as any other OTC in deciding~~ and ~~whether to~~ provide it at no cost. carry JPK nevertheless,

B. Gastrointestinal-1 (GI-1) Drug Class—Mesalamine (Asacol)

The GI-1 Drug Class was previously reviewed by the P&T Committee in February 2011. Mesalamine delayed release tablets (Asacol) were designated as BCF. In March 2013, Asacol tablets were discontinued by the manufacturer, Warner Chilcott, and supplies have been depleted. Warner Chilcott subsequently received FDA approval for a new formulation, Delzicol capsules, which is substantially more costly than Asacol.

Several other mesalamine delayed release tablets are on the UF, including Asacol HD, Apriso, Lialda, and Pentasa. These products use different proprietary methods to delay release of the drug into the large intestine and, therefore, are not interchangeable and have different FDA-approved indications and dosing.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) upon signing of the minutes, to:
   a) remove mesalamine delayed release tablets (Asacol) from the BCF.
   b) The GI-1 Drug Class will not have a designated BCF product until the class can be re-reviewed for UF status. MTFs are advised to order what they need to meet local needs.

VII. UTILIZATION MANAGEMENT

A. PA

1. **Injectable Gonadotropins**—In November 2012, PA criteria for the injectable gonadotropins was revised to allow for use in conjunction with a noncoital reproductive technology, as outlined in the ASD(HA) April 2012 "Policy for Assisted Reproductive Services for the Benefit of Seriously or Severely Ill/Injured (Category II or III) Active Duty Service Members." A Signed Authorization Memorandum from TMA must be included with the prescription, and a new prescription is required for each assisted reproductive technology (ART) cycle. The P&T Committee clarified the PA criteria to set a 60-day expiration date for the PA, to help ensure that an authorization memorandum is included with each ART cycle. A 60-day expiration is sufficient for a patient to complete an ART cycle.

   a) ***COMMITTEE ACTION: INJECTABLE GONADOTROPINS***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) clarifying the existing PA criteria for the injectable gonadotropins to have a 60-day expiration date for the PA.

2. **Proton Pump Inhibitors (PPIs): Pantoprazole Change from Non-Preferred to Step-Preferred Status**—The PPIs currently have PA criteria (step therapy) requiring a trial of omeprazole or esomeprazole (Nexium) prior to use of the other PPIs. Omeprazole and esomeprazole are BCF and step-preferred. In November 2012, the P&T Committee

recommended reclassification of pantoprazole as formulary on the UF, due to availability of cost-effective generic formulations; pantoprazole remained non-preferred. The other PPIs, lansoprazole (Prevacid), rabeprazole (Aciphex), and omeprazole/sodium bicarbonate (Zegerid), are NF and non-preferred. The cost of generic pantoprazole tablets has continued to decline since November 2012. The P&T Committee recommended revising the PA criteria to designate pantoprazole as step-preferred (i.e., in front of the step).

a) ***COMMITTEE ACTION: PANTOPRAZOLE PA CRITERIA/ STEP-PREFERRED STATUS***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) designating pantoprazole as step-preferred (i.e., in front of the step) on the UF.

3. **Antilipidemics-2: Icosapent ethyl (Vascepa)**—Icosapent ethyl (Vascepa) is the second prescription fish oil product marketed. Icosapent ethyl has the same FDA-approved labeling and dosing as omega-3-acid ethyl esters (Lovaza). Vascepa is not as effective as Lovaza at lowering triglycerides, but does not adversely affect LDL levels. PA criteria apply to Lovaza, limiting use to the FDA-approved indications, due to the large number of off-label, non-supportable uses. The P&T Committee recommended manual PA criteria for all current and new users of Vascepa, limiting use to the FDA-approved indication; the manual PA criteria for Vascepa will be the same as criteria for Lovaza.

   a) ***COMMITTEE ACTION: ICOSAPENT ETHYL (VASCEPA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) manual PA criteria for all current and new users of Vascepa, limiting use to the FDA-approved indication. (See Appendix C for full criteria.)

4. **Abiraterone (Zytiga)**— Zytiga is an inhibitor of CYP 17 (an enzyme expressed in testicular, adrenal, and prostatic tumor tissues that is required for androgen biosynthesis). PA criteria for abiraterone (Zytiga) were recommended at the November 2012 meeting, consistent with the FDA labeling. At that time, Zytiga was FDA-approved for treatment of patients with metastatic castration-resistant prostate cancer who had previously received docetaxel. The FDA has subsequently updated the approved labeling for patients with metastatic castration-resistant prostate cancer with concomitant prednisone.

a) ***COMMITTEE ACTION: ABIRATERONE (ZYTIGA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the abiraterone (Zytiga) PA criteria for use in patients with a documented diagnosis of metastatic castration-resistant prostate cancer on concomitant prednisone. The previous criterion for prior chemotherapy containing docetaxel is no longer required.

B. Quantity Limits (QLs)

1. **Oral tretinoin 10 mg capsules (Vesanoid)**—Oral tretinoin 10 mg capsules are approved for inducing remission in acute promyelocytic leukemia. The product was previously available under the trade name Vesanoid, but now only generic formulations are available. Quantity limits are in place for several oral chemotherapy agents. The P&T Committee recommended QLs for oral tretinoin 10 mg capsules due to the high cost and adverse event profile.

a) ***COMMITTEE ACTION: ORAL TRETINOIN 10MG CAPSULES (VESANOID) QLs***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) QLs/days supply limits for oral tretinoin 10 mg capsules (Vesanoid), based on FDA-approved labeling, limiting use to a 30-day supply in the Retail Network, and a 45-day supply in the Mail Order.

VIII. ADJOURNMENT

The meeting adjourned at 1630 hours on May 15, 2013. The next meeting will be in August 2013.

Appendix A—Attendance: May 2013 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix E—Table of Abbreviations

Appendix A—Attendance: May 2013 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Peter Bulatao, MS for COL John Spain, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CDR Aaron Middlekauf for CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
COL Ted Cieslak, MC	Army, Physician at Large
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
COL Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Jeremy King, MC	Air Force, OB/GYN Physician
LCDR Christine Olsen, MC	Navy, Pediatrics
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
COL Todd Williams, MS	Defense Medical Materiel Program Office
Maj Dan Castiglia via DCO	Defense Logistics Agency Troop Support
Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
CAPT Joel A. Roos	Navy Medicine Training Support Center
LCDR David Sohl	University of Texas Masters Student
Maj Ellen Roska	University of Texas PhD Student

Appendix A—Attendance (continued)

Others Present	
LCDR Marisol Martinez, USPHS	DoD Pharmacoeconomic Center
LCDR Joshua Devine, USPHS	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Linh Quach, MSC	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe via DCO	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
LT Kendra Jenkins, USPHS	Pharmacy Resident
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Mr. Kirk Stocker	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Canagliflozin (Invokana) **Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**	• Use of the formulary agent is contraindicated
• Febuxostat (Uloric) **Anti-gout Drugs**	• Use of allopurinol is contraindicated. • The patient has experienced significant adverse effects from allopurinol that are not expected to occur with the non-formulary medication. • Use of allopurinol has resulted in therapeutic failure. • The patient previously responded to non-formulary agent and changing to allopurinol would incur unacceptable risk.

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Canagliflozin (Invokana) **Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**	All new and current users of an SLGPT2 inhibitor are required to try metformin, a sulfonylurea (SU), or a DPP-4 inhibitor before receiving canagliflozin (Invokana). Automated PA criteria—The patient has filled a prescription for metformin, a SU, or a DPP-4 inhibitor at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA criteria—If automated criteria are not met, canagliflozin (SGLT2 inhibitor) is approved (e.g., trial of metformin or SU or DPP-4 inhibitor is NOT required) if: • The patient has experienced any of the following issues on metformin: o impaired renal function precluding treatment with metformin o history of lactic acidosis • The patient has experienced any of the following issues on a sulfonylurea: o hypoglycemia requiring medical treatment • The patient has had inadequate response to metformin or a SU or a DPP-4 inhibitor • The patient has a contraindication to metformin or a SU or DPP-4 inhibitor
• Febuxostat (Uloric) **Anti-gout Drugs**	New and current users of febuxostat (Uloric) are required to try allopurinol. Automated PA Criteria—The patient has received a prescription for allopurinol at any Military Health System pharmacy point service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days. AND Manual PA Criteria—If automated criteria are not met, febuxostat (Uloric) is approved (e.g., a trial of allopurinol is not required) if: • The patient has experienced any of the following issues with at least one of the following with allopurinol, which is not expected to occur with febuxostat (Uloric): o The patient has had an inadequate response to allopurinol (failure to achieve serum uric acid levels < 6 mg/day) after an adequate trial (at least 300 mg per day of allopurinol) o The patient has had intolerable adverse effects (e.g., hypersensitivity) to allopurinol o The patient has a contraindication to allopurinol (e.g., renal impairment)

• icosapent ethyl (Vascepa) **Antilipidemic-2s**	New and current users of Vascepa are required to undergo the PA process. <u>Manual PA Criteria</u>—Vascepa is approved if: • Patients Receiving Statins: o Patients with triglyceride (TG) Levels > 500 mg/dL AND o Inadequate TG-lowering response to a therapeutic trial of niacin (1-g/day), unable to tolerate niacin/fibrate or who are not a candidate for niacin/fibrate therapy * ** • Patients NOT Receiving Statins: o Patients with TG Levels > 500 mg/dL AND o Inadequate response to a therapeutic trial of monotherapy with both a fibrate and niacin (1-2 g/day), unable to tolerate a fibrate and niacin or who are not candidates for fibrates** and niacin therapy • Patients with TG <500 mg/dL or <500 mg/dL with an inadequate TG-lowering response to niacin or fibrates or who are unable to tolerate/are not candidates for niacin or fibrates • Coverage is not approved for the use of Vascepa for the treatment of other conditions, including: ADHD, Alzheimer's disease, bipolar disorder, Crohn's disease, cystic fibrosis, dementia, depression, inflammatory bowel disease, intermittent claudication, metabolic syndrome, osteoporosis, PTSD, renal disease (IgA nephropathy), rheumatoid arthritis, schizophrenia, Type 2 diabetes mellitus, and ulcerative colitis *Not candidates for niacin: patients with a history of confirmed PUD (perforation, ulceration, or upper GIB), gouty attacks (presence of intra-articular uric acid crystals in the affected joint), and/or poorly controlled diabetes **Not candidates for fibrates: patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis and preexisting gallbladder disease
• abiraterone (Zytiga) **Oral Chemotherapy Drugs for Prostate Cancer**	<u>Manual PA Criteria</u>—Coverage approved for treatment of patients: • With a documented diagnosis of metastatic castration-resistant prostate cancer AND • Patient is receiving concomitant prednisone

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2013	**Pulmonary II Drugs**	UF Class Review	▪ Ipratropium HFA MDI (Atrovent HFA) ▪ Ipratropium/ albuterol nebulized solution (DuoNeb) ▪ Tiotropium inhaler (Spiriva)	▪ Aclidinium inhaler (Tudorza) ▪ Ipratropium nebulized solution (Atrovent) ▪ Ipratropium / albuterol soft mist inhaler (Combivent Respimat) ▪ Roflumilast (Daliresp)	▪ None	Pending signing of the minutes	None	▪ Combivent Respimat added to the BCF
May 2013	**Anti-Gout Drugs**	UF class review	▪ Allopurinol	▪ colchicine (Colcrys) ▪ probenecid ▪ colchicine/probenecid	▪ Febuxostat (Uloric)	Pending signing of the minutes / 90 days	Step therapy (automated PA); requires a trial of allopurinol prior to use of Uloric in all new and current users of Uloric.	▪ Step therapy does not apply to colchicine, probenecid, or colchicine/ probenecid
May 2013	**Non-Insulin Diabetes Drugs: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**	New Drug review	▪ None	▪ None	▪ **Canagliflozin (Invokana) recommended for NF May 2013**	Pending signing of the minutes / 30 days	Step therapy (automated PA); requires a trial of metformin, an SU, or a DPP-4 inhibitor in all new and current users of a SGLT2 inhibitor	BCF, UF, and NF drugs are designated for the non-insulin diabetes drugs for metformin, sulfonylureas, DPP-4 inhibitors, GLP1RA agonists, TZDs, meglitinides, and alpha glucosidase inhibitors (see Minutes November 2010, August 2012, and November 2012).

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix E—Table of Abbreviations

ASD(HA)	Assistant Secretary of Defense for Health Affairs
ART	assisted reproductive technology
BCF	Basic Core Formulary
BIA	budget impact analysis
CFC	chlorofluorocarbon
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DCO	Defense Connect Online
DoD	Department of Defense
DPP-4	dipeptidyl-dipeptidase-4
EMA	European Medicines Association
FDA	U.S. Food and Drug Administration
GI-1	Gastrointestinal-1 Drug Class
GLP1RA	glucagon-like peptide-1 receptor agonist
HFA	hydrofluoroalkane
LAMA	long-acting muscarinic agent
LDL	low-density lipoprotein cholesterol
MDI	metered dose inhaler
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
NSAIDs	nonsteroidal anti-inflammatory drugs
OTC	over-the-counter
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE-4	phosphodiesterase-4
PEC	Pharmacoeconomic Center
POS	points of service
PPIs	proton pump inhibitors
QLs	quantity limits
SABA	short-acting beta agonist
SAMA	short-acting muscarinic agent
SGLT2	sodium glucose co-transporter 2
SMBGS	self-monitoring blood glucose system
SU	sulfonylurea
sUA	serum uric acid
TG	triglyceride
TZD	thiazolidinedione
ULT	urate-lowering therapy
UF	Uniform Formulary

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

February 2013

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Newer Sedative Hypnotic-1 (SED-1s) Agents—Zolpidem Sublingual Low-Dose Tablets (Intermezzo)

Relative Clinical Effectiveness Conclusion—Intermezzo is a new low-dose zolpidem sublingual (SL) formulation available in 1.75 mg and 3.5 mg tablets. The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that despite its unique FDA labeling for middle-of-the-night awakening compared to the other SED-1s and the potential for less next-day impairment, zolpidem SL low dose (Intermezzo) does not offer a clinically compelling advantage over the other SED-1s included on the Uniform Formulary (UF).

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that zolpidem SL low dose (Intermezzo) is not cost-effective when compared to other SED-1s included on the UF. The relative cost minimization analysis (CMA) ranking of the comparator SED-1s (ranked from most cost-effective to least cost-effective) revealed that zolpidem immediate release (IR) (Ambien IR, generics) < zaleplon (Sonata, generics) < zolpidem ER (Ambien CR, generics) < zolpidem SL (Edluar)< ramelteon (Rozerem) < zolpidem SL low dose (Intermezzo).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) zolpidem sublingual low dose (Intermezzo) be designated nonformulary (NF) due to the lack of compelling clinical advantages and cost disadvantage compared to UF products.

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***
The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following MN criteria for zolpidem SL low dose (Intermezzo): there is no alternative formulary agent—the patient has swallowing difficulties and requires a product for middle-of-the-night awakening.

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
Existing automated prior authorization (step therapy) requires a trial of generic zolpidem IR or zaleplon, the step-preferred agents, prior to the other SED-1s in new users. The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following PA criteria should apply to Intermezzo. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria: The patient has filled a prescription for zolpidem IR or zaleplon at any Military Health System (MHS) pharmacy point of service (POS) [military treatment facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

   b) Manual PA criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is July 17, 2013.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

II. UF DRUG CLASS REVIEWS

A. Topical Pain Agents

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Lidocaine 5% patch (Lidoderm) is effective for the management of its orphan indication, postherpetic neuralgia (PHN). There is insufficient evidence supporting use of Lidoderm for other neuropathies (e.g., diabetic neuropathy, HIV-associated neuropathy, complex regional pain syndrome); however, several professional guidelines support its use. There is a paucity of data regarding use

of Lidoderm for other off-label conditions, including widespread or deep pain conditions such as fibromyalgia or chronic pain associated with osteoarthritis.

- A review of MHS prescribing trends showed a high discontinuation rate for Lidoderm, with a similar prevalence between unique user new starts and discontinuations. A Pharmacy Outcomes Research Team (PORT) analysis showed that Lidoderm is commonly prescribed in the MHS for off-label, non-supportable uses (e.g., musculoskeletal pain) that are not associated with neuropathic pain.
- There are no head-to-head trials comparing the topical diclofenac products (Voltaren gel, Pennsaid drops, and Flector patch) in terms of efficacy or safety. However, indirect evidence suggests the agents are highly interchangeable with regard to efficacy. Limited evidence suggests the agents are as effective as oral diclofenac.
- The incidence of gastrointestinal (GI) adverse events is lower with the topical diclofenac products compared to oral nonsteroidal anti-inflammatory drugs (NSAIDs), offering a potential advantage for patients with a history of GI bleeding or peptic ulcers.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that among topical diclofenac products, diclofenac gel (Voltaren) was the most cost-effective, based on the weighted average cost per day of treatment across all three POS, followed by diclofenac drops (Pennsaid) and diclofenac patch (Flector). Results from the CMA and budget impact analyses (BIAs) showed that the scenario where Lidocaine patch (Lidoderm) and diclofenac gel (Voltaren) were designated UF, with diclofenac drops (Pennsaid) and patch (Flector) designated NF, was the most cost-effective for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) lidocaine 5% patch (Lidoderm) and diclofenac 1% gel (Voltaren) remain designated with formulary status on the UF, and recommended NF status for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector), based on clinical and cost effectiveness.
2. ***COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) that none of the topical pain agents be designated BCF. Because the topical pain agents are a subclass of the Pain Agents, there is no requirement to designate a topical agent with BCF status. Several pain agents (narcotic analgesics and oral NSAIDs) are included on the BCF. The cost-effectiveness analysis revealed no financial benefit to the MHS for placement of the topical pain agents on the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) MN criteria for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector). (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—After extensive discussion, the P&T Committee recommended (12 for, 4 opposed, 1 abstained, 0 absent) manual PA criteria apply to all current and new users of lidocaine 5% patch (Lidoderm). Coverage is approved for patients who have a diagnosis of postherpetic neuralgia, other peripheral neuropathic pain, and for patients with non-neuropathic pain where an occupational or clinical reason exists and other analgesics are contraindicated. Coverage is not approved for other uses of Lidoderm. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is August 14, 2013.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Pulmonary II Drugs

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Aclidinium inhaler (Tudorza) is the second long-acting muscarinic agent (LAMA) on the market. The three clinical trials used to obtain FDA approval reported statistically significant improvement in spirometric endpoints, and two of the trials reported significantly fewer chronic obstructive pulmonary disease (COPD) exacerbations with aclidinium, compared to placebo.
- For aclidinium, the adverse event profile appears minimal, with primarily anticholinergic events reported. However, there is limited safety data with the 400 mcg approved dose. The FDA is requiring a prospective clinical trial to

assess cardiovascular safety. Longer duration and larger comparative trials are needed to determine aclidinium's place in therapy.

- Several trials have shown the LAMA tiotropium (Spiriva) is associated with clinically significant improvements in spirometric endpoints and reductions in risk for COPD exacerbations. Tiotropium is also reported to reduce the proportion of patients hospitalized for COPD exacerbations.

- Reports of a possible link between tiotropium and adverse cardiovascular (CV) events including death, stroke, and myocardial infarction have not been confirmed in prospective trials.

- Roflumilast (Daliresp) is the first oral selective inhibitor of phosphodiesterase type 4 marketed in the United States. Its FDA indication is limited to reducing the incidence of COPD exacerbations in patients with severe COPD. In two clinical trials, roflumilast was associated with statistically significant reductions in the rate of COPD exacerbations.

- For roflumilast, safety issues identified by the FDA included psychiatric events (including suicide), weight loss, GI upset and severe diarrhea, and nasal tumors. However, the FDA did not require additional prospective safety studies. A risk evaluation and mitigation strategy program was not required.

- Albuterol/ipratropium inhaler (Combivent Respimat) is the new propellant-free inhaler that is replacing the ozone-depleting chlorofluorocarbon (CFC)-containing Combivent metered dose inhaler (MDI). The clinical trial used to obtain FDA approval showed Combivent Respimat was non-inferior to Combivent CFC MDI in terms of improvements in spirometric endpoints.

Relative Cost-Effectiveness Conclusion—The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

C. Oral Anticoagulants

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following for warfarin, dabigatran (Pradaxa), and rivaroxaban (Xarelto). Apixaban (Eliquis) will be reviewed at an upcoming P&T meeting due to recent FDA approval in late 2012.

- The newer oral anticoagulants (NOACs) dabigatran and rivaroxaban have advantages of predictable anticoagulant effect, fixed dosing, and fewer drug interactions compared to warfarin (Coumadin, generic). Advantages of warfarin

include its long history of use, reliable reversal agent (vitamin K), and adverse effects that are predictable and manageable.

- The NOACs offer a convenience to patients; laboratory monitoring for efficacy and dietary restrictions are not required. More data is needed in patients with renal and hepatic impairment. No reversal agent is available with the NOACs.
- In non-valvular atrial fibrillation (Afib), dabigatran and apixaban were superior to poorly controlled warfarin at preventing stroke and systemic embolism, including hemorrhagic stroke; rivaroxaban was non-inferior to poorly controlled warfarin for these outcomes. Intracranial bleeding was lower with dabigatran, rivaroxaban, and apixaban compared to warfarin.
- For venous thromboembolism (VTE) prevention following orthopedic surgery, rivaroxaban was superior to enoxaparin at preventing symptomatic deep venous thrombosis (DVT), but at the cost of increased bleeding. For prevention of VTE recurrence following DVT or pulmonary embolism (PE), rivaroxaban in two trials was non-inferior to enoxaparin/warfarin for preventing recurrent VTE, with no difference in bleeding, and was superior to placebo in one trial for extended therapy for 6–12 months.
- Due to a lack of head-to-head trials, there is insufficient evidence to determine if one NOAC has advantages over the others.
- Patients require education and clinical monitoring to ensure appropriate use and avoid adverse reactions with the NOACs. Bleeding is a concern with all the NOACs, and dabigatran is associated with dyspepsia and major GI bleeding. For warfarin, a high risk of falls is not associated with risk of subsequent major bleeding.
- It remains to be determined whether the NOACs will increase the numbers of patients currently undertreated for stroke prevention in Afib. Also unknown is whether NOACs will improve persistence rates for anticoagulation therapy.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Anticoagulant agents for stroke prevention in non-valvular AFib—CMA results showed that, in all scenarios, warfarin, including drug monitoring costs, was the least costly agent. Cost-effectiveness analysis (CEA) results showed that the incremental cost-effectiveness ratios per life year gained with dabigatran and rivaroxaban in relation to warfarin were in a range that could be considered cost-effective to the MHS.
- Anticoagulant agents for DVT/PE prophylaxis in hip and knee replacement surgery—CMA results demonstrated that rivaroxaban was a cost-effective

alternative compared to enoxaparin, based on analysis of the average weighted price per day of therapy at all three POS.

- BIA results—Scenarios where all drugs remain on the UF resulted in the greatest cost-avoidance to the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) warfarin (Coumadin, generic), dabigatran (Pradaxa), and rivaroxaban (Xarelto) remain formulary on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) maintaining warfarin (Coumadin, generic) on the BCF. MTFs are highly encouraged to purchase the contracted warfarin generic product.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

III. UTILIZATION MANAGEMENT

A. PA

1. **Tretinoin Age Limits**—The P&T Committee reviewed the current age limits for tretinoin, which does not allow use in patients older than 35 years. While treatment for acne is covered by TRICARE benefits, cosmetic services and supplies are excluded from the benefit, including treatments for photoaging of the skin.

   a) ***COMMITTEE ACTION: TRETINOIN AGE LIMITS***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) removing the age limit for tretinoin products that are not exclusively labeled for cosmetic use at all 3 MHS POS (MTF, Mail Order, and the Retail Network). Acne can occur beyond age 35. Treatment for acne is covered by TRICARE benefits and low-cost tretinoin generic formulations are available. Tretinoin products/derivatives specifically indicated for cosmetic use as a result of the aging process (e.g., Renova, Refissa, Avage) remain excluded from the Pharmacy benefit.

2. **Zolpidem Gender-Based Dosing**—The P&T Committee discussed whether PA criteria are needed for zolpidem products, given new recommendations from the FDA in January 2013 regarding dosing in women. For women, lower dosing is recommended, as blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. A review of MHS prescriptions in the last six months of 2012 showed significant use of the higher zolpidem dosages in women.

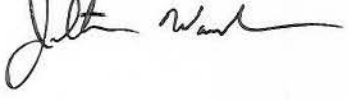
    a) ***COMMITTEE ACTION: ZOLPIDEM GENDER-BASED DOSING*** The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) to not institute gender-based dosing PA criteria for zolpidem products, and to instead educate providers of the new recommendations, and notify patients via beneficiary newsletters of the concerns regarding impaired driving and activities requiring mental alertness the morning after use. The P&T Committee recommended re-evaluating this issue in six months to review MHS prescribing trends and whether additional measures are necessary.

B. Quantity Limits (QLs)

1. The P&T Committee reviewed quantity limit proposals for four products: aclidinium oral inhaler (Tudorza) for COPD, beclomethasone dipropionate nasal inhaler (Qnasl) for seasonal and perennial allergic rhinitis, ponatinib (Iclusig) tablets for treatment of patients with chronic myelogenous leukemia (CML), and cabozantinib (Cometriq) for patients with progressive, metastatic medullary thyroid cancer. QLs are recommended due to either existing QLs in the class to prevent wastage (inhalers) or due to high cost/adverse event profiles with subsequent need for dosage changes.

    a) ***COMMITTEE ACTION: ACLIDINIUM (TUDORZA), BECLOMETHASONE (QNASAL), PONATINIB (ICLUSIG) and CABOZANTINIB (COMETRIQ) QLs***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) QLs for aclidinium oral inhaler (Tudorza), beclomethasone dipropionate nasal inhaler (Qnasl), ponatinib tablets (Iclusig), and cabozantinib (Cometriq), based on FDA-approved labeling. (See Appendix D.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved



Approved, but modified as follows:

VI. ITEMS FOR INFORMATION

A. Options for Future DoD P&T Committee Meetings—Given the current budget restrictions regarding travel, the P&T Committee discussed options for future meetings, including Defense Connect Online (DCO) web conferences. Items of concern voiced by the P&T Committee if DCO teleconferences were implemented in lieu of in-person meetings included maintaining confidentiality of the contracted pricing solicitations, likelihood of interruption/inattention, decreased engagement by P&T Committee members, and potential lost opportunities for cost-avoidance, which would ultimately negatively impact TRICARE beneficiaries.

B. Cost-Effectiveness Modeling Review—The P&T Committee reviewed an analysis of previous UF economic evaluations that compared the performance of cost modeling projections and budget impact analyses to actual observed costs in the MHS. Overall, the evaluated cost-effectiveness models performed suitably, demonstrating expenditure and utilization trends that were similar between modeled outcomes and actual results. Possible factors contributing to variance between the modeled outcomes and actual results were discussed. Potential improvements identified during the review will be incorporated into future cost modeling scenarios and processes.

C. Smoking Cessation Program Final Rule—As of the meeting date, the Smoking Cessation Final Rule has not yet been published in the Code of Federal Regulations. The Proposed Rule provides that smoking cessation pharmaceutical agents, including FDA-approved over-the-counter pharmaceutical agents, will be available through the TRICARE Mail Order Pharmacy or the MTF. Until publication of the Final Rule, all UF/BCF recommendations for smoking cessation products from the May 2012 DoD P&T Committee meeting remain on hold.

D. POS Analysis Update—The PORT provided an update on MHS prescribing trends by point of service. The results showed that for branded medications considered maintenance products (e.g., used for chronic conditions and not specialty medications), drug costs (30-day equivalent prescriptions) would have been about 27%–31% lower, if all prescriptions that were filled and dispensed in the Retail Network had instead been dispensed at the MTFs or at the Mail Order. In contrast, drug costs would have been about 13%–18% higher if generic drugs dispensed in the Retail Network had instead been dispensed in the MTFs or Mail Order.

E. **New TRICARE Pharmacy Copayments**—The P&T Committee was briefed on new pharmacy co-pays that were implemented in February 2013. At the Mail Order POS, co-pays for Tier 1 drugs (generics) remain $0, with co-pays of $13 for Tier 2 products (preferred brands) and $43 for Tier 3 products (non-preferred brands). The new co-pays in the Retail Network are $5 (Tier 1), $17 (Tier 2) and $44 (Tier 3). In the Mail Order, one co-pay applies for up to a 90-day supply, and one co-pay applies for up to a 30-day supply in the Retail Network.

F. **Step Therapy Safety Net**—The P&T Committee was briefed on the Rapid Response Step Therapy "Safety Net" Program implemented in September 2012. The program was initiated to educate beneficiaries affected by a step therapy reject and to educate providers regarding step-preferred drugs. The program targets beneficiaries who have not received a prescription fill for either a step-preferred or non step-preferred drug, after the initial reject. Since implementation, the MHS successful cases averaged 38.30%, which is similar to successful cases reported in commercial programs. Updates on the program will be periodically provided to the P&T Committee.

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

13 May 2013
Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

February 2013

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 20 and 21, 2013, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of November 2012 Minutes**—Jonathon Woodson M.D., Director, approved the minutes for the November 2012 DoD P&T Committee meeting on February 13, 2013.
2. **Clarification to the November 2012 Minutes—Prior Authorization (PA) Implementation Date for enzalutamide (Xtandi) and abiratone (Zytiga):** The November minutes were clarified to state March 20, 2013, is the effective implementation date for PA criteria applicable to enzalutamide (Xtandi) and abiratone (Zytiga).

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Newer Sedative Hypnotic-1 (SED-1s) Agents—Zolpidem Sublingual Low Dose Tablets (Intermezzo)

Relative Clinical Effectiveness—Intermezzo is a new low-dose zolpidem sublingual

(SL) formulation available in 1.75 mg and 3.5 mg tablets. Women should not receive Intermezzo doses larger than 1.75 mg. Intermezzo is specifically approved for treatment of insomnia characterized by middle-of-the-night waking followed by difficulty returning to sleep. In one study, there was a statistically significant improvement in sleep latency and total sleep time with Intermezzo versus placebo for middle-of-the-night awakening, but another placebo-controlled trial found no differences in total sleep time. No studies have been completed with an active comparator.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) despite its unique FDA labeling for middle-of-the-night awakening compared to the other SED-1s and the potential for less next-day impairment, zolpidem SL low dose (Intermezzo) does not offer a clinically compelling advantage over the other SED-1s included on the UF.

Relative Cost-Effectiveness Analysis and Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that zolpidem SL low dose (Intermezzo) is not cost-effective when compared to other SED-1s included on the UF. The relative cost minimization analysis (CMA) ranking of the comparator SED-1s (ranked from most cost-effective to least cost-effective) revealed that zolpidem immediate release (IR) (Ambien IR, generics) < zaleplon (Sonata, generics) < zolpidem ER (Ambien CR, generics) < zolpidem SL (Edluar)< ramelteon (Rozerem) < zolpidem SL low dose (Intermezzo).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) zolpidem sublingual low dose (Intermezzo) be designated NF due to the lack of compelling clinical advantages and cost disadvantage compared to UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following MN criteria for zolpidem SL low dose (Intermezzo): there is no alternative formulary agent—the patient has swallowing difficulties and requires a product for middle-of-the-night awakening.

3. ***COMMITTEE ACTION: PA CRITERIA***—Existing automated prior authorization (step therapy) requires a trial of generic zolpidem IR or zaleplon, the step-preferred agents, prior to the other SED-1s in new users. The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following PA criteria should apply to Intermezzo. Coverage would be approved if the patient met any of the following criteria:

a) Automated PA criteria: The patient has filled a prescription for zolpidem IR or zaleplon at any Military Health System (MHS) pharmacy point of service (POS) [military treatment facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

b) Manual PA criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is July 17, 2013.

V. UF DRUG CLASS REVIEWS

A. Topical Pain Agents

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the Topical Pain agents subclass, which is comprised of lidocaine 5% patch (Lidoderm), diclofenac 1% gel (Voltaren), diclofenac 1.5% solution (Pennsaid), and diclofenac 1.3% patch (Flector).

The Topical Pain agents are a subclass of the Pain Agents UF drug class, which includes the Narcotic Analgesics and oral Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Extensive review of the literature provided limited evidence regarding efficacy and safety of the topical pain agents.
- Lidoderm is effective as first line and/or combination therapy for the management of its orphan indication—postherpetic neuralgia (PHN). There is insufficient evidence supporting use of Lidoderm for other neuropathies (e.g., diabetic neuropathy, HIV-associated neuropathy, complex regional pain syndrome); however, several professional guidelines support its use. There is a paucity of data regarding use of Lidoderm for other off-label conditions, including widespread or deep pain conditions such as fibromyalgia or chronic pain associated with osteoarthritis.

- A review of MHS prescribing trends showed a high discontinuation rate for Lidoderm, with a similar prevalence between unique user new starts and discontinuations.
- Topical diclofenac formulations (Voltaren gel, Pennsaid drops, and Flector patch) are effective in managing superficial pain associated with osteoarthritis of the knee and wrist, and superficial pain associated with sprains, strains, and contusions.
- There are no head-to-head trials comparing the topical diclofenac products in terms of efficacy or safety. However, indirect evidence suggests the agents are highly interchangeable with regard to efficacy. Limited evidence suggests the agents are as effective as oral diclofenac.
- The incidence of gastrointestinal (GI) adverse events is lower with the topical diclofenac products compared to oral NSAIDs, offering a potential advantage for patients with a history of GI bleeding or peptic ulcers.
- Systemic side effects are uncommon and the most common adverse events are application site reactions, including pruritis with Lidoderm, and dry skin, erythema and pruritis with the topical diclofenac products.
- Flector is indicated for short-term use associated with acute musculoskeletal injury and is likely to be used in a younger population than Voltaren gel or Pennsaid drops.
- Pennsaid is indicated only for osteoarthritis of the knee and clinical usefulness may be limited by multiple daily dosing (four times daily).
- A Pharmacy Outcomes Research Team (PORT) analysis reviewing ICD-9 codes associated with Lidoderm prescriptions in the MHS revealed significant overlap for diagnoses associated with neuropathic and musculoskeletal pain. Only 3% of prescriptions were written for patients with the FDA-approved PHN indication. Up to 49% of patients receiving Lidoderm prescriptions had no neuropathic diagnosis: 39% had musculoskeletal diagnoses without neuropathic diagnoses and 10% had neither neuropathic nor musculoskeletal diagnostic codes. This suggests that Lidoderm is commonly used in the MHS for off-label use that is not associated with neuropathic pain.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses were performed for the Topical Pain Agent subclass, including CMA and budget impact analyses (BIAs). For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that among topical diclofenac products, diclofenac gel (Voltaren) was the most cost-effective, based

on the weighted average cost per day of treatment across all three POS, followed by diclofenac drops (Pennsaid), and diclofenac patch (Flector). Results from the CMA and BIAs showed that the scenario where Lidocaine patch (Lidoderm) and diclofenac gel (Voltaren) were designated UF, with diclofenac drops (Pennsaid) and patch (Flector) designated NF, was the most cost-effective for the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) lidocaine 5% patch (Lidoderm) and diclofenac 1% gel (Voltaren) remain designated with formulary status on the UF, and recommended NF status for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector), based on clinical and cost effectiveness.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) that none of the topical pain agents be designated BCF. Because the topical pain agents are a subclass of the Pain Agents, there is no requirement to designate a topical agent with BCF status. Several pain agents (narcotic analgesics and oral NSAIDs) are included on the BCF. The cost-effectiveness analysis revealed no financial benefit to the MHS for placement of the topical pain agents on the BCF.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) MN criteria for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector). (See Appendix B for full MN criteria.)

4. ***COMMITTEE ACTION: PA CRITERIA***—After extensive discussion, the P&T Committee recommended (12 for, 4 opposed, 1 abstained, 0 absent) manual PA criteria apply to all current and new users of lidocaine 5% patch (Lidoderm). Coverage is approved for patients who have a diagnosis of postherpetic neuralgia, other peripheral neuropathic pain, and for patients with non-neuropathic pain where an occupational or clinical reason exists and other analgesics are contraindicated. Coverage is not approved for other uses of Lidoderm. (See Appendix C for full criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions. Based on the P&T Committee's recommendation, the effective date is August 14, 2013.

B. Pulmonary II Drugs

Background and Relative Clinical Effectiveness—The Pulmonary II Drug Class is comprised of aclidinium inhaler (Tudorza), tiotropium inhaler (Spiriva), roflumilast tablets (Daliresp), ipratropium (Atrovent HFA inhaler; Atrovent nebulized solution), and ipratropium/albuterol (Combivent, Combivent Respimat and DuoNeb nebulized solution). The two inhalation solutions, ipratropium (Atrovent) and ipratropium/ albuterol (DuoNeb), are available in generic formulations.

Combivent metered dose inhaler (MDI) is one of the last available chlorofluorocarbon (CFC) MDIs on the market and will have supplies exhausted by December 2013. Its replacement is Combivent Respimat, a new CFC- and propellant-free formulation.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- With regard to the long-acting muscarinic agents (LAMAs), aclidinium (Tudorza) and tiotropium (Spiriva), and the short-acting muscarinic agent (SAMA), ipratropium (Atrovent HFA), the P&T Committee concluded the following:
  - Aclidinium (Tudorza) is a dry powder inhaler (DPI) administered twice daily. The three clinical trials used to obtain FDA approval reported statistically significant improvement in lung function/spirometric endpoints [forced expiratory volume in 1 second (FEV_1)] compared with placebo at 12 weeks. Two of the trials reported statistically significant reductions in chronic obstructive pulmonary disease (COPD) exacerbations versus placebo.
  - In a small-dose ranging trial with 30 participants lasting for 15 days, there was no significant difference between aclidinium and tiotropium in terms of improvements in spirometric endpoints (FEV_1).
  - For aclidinium, the adverse event profile appears minimal, with primarily anticholinergic events reported. However, there is limited safety data with the approved 400 mcg dose. The FDA is requiring a prospective clinical trial to assess cardiovascular (CV) safety. Longer duration and larger comparative trials are needed to determine aclidinium's place in therapy.
  - Tiotropium is formulated as a DPI administered once daily. Several trials have documented tiotropium is associated with clinically significant improvements in FEV_1 and forced vital capacity compared with placebo or ipratropium. Additional benefits include reductions in the risk for COPD exacerbations as well as reduced hospitalizations due to COPD exacerbations.
  - Reports of a possible link between tiotropium and adverse CV events including death, stroke, and myocardial infarction (MI) were first raised in

2008, based on meta-analysis and retrospective analyses of health claims data. New data based on a large 4-year prospective trial (UPLIFT) and other analyses does not support an association with tiotropium and CV adverse events.

  - The other common adverse effects of tiotropium are anticholinergic in nature. There are reports of incorrect administration of the inhaler, with patients swallowing the capsule, instead of administering it via the HandiHaler device.
  - Ipratropium has been marketed since 1995. Review of the clinical literature for efficacy did not add substantial new information. For safety, while there may be a possible signal between ipratropium use and CV adverse events, the data is limited due to study design (cohort studies), influence of underlying CV disease, and presence of underlying pulmonary cancers.

- With regard to the SAMA/LAMA combination products, Combivent Respimat demonstrated similar improvements in FEV_1 as Combivent CFC MDI in the clinical trial used to obtain FDA approval. Some older patients or those with hand joint problems may require assistance for the initial assembly of the Combivent Respimat inhaler and cartridge. Combining bronchodilators may improve efficacy and decrease the risk of side effects, as compared to maximizing the dose of a single bronchodilator, and also provide a convenience to the patient. The safety profile of Combivent Respimat is similar to Combivent CFC MDI.
- Roflumilast (Daliresp) is the first oral phosphodiesterase type 4 inhibitor marketed in the United States, and is administered once daily. It has a narrow FDA indication, limited to reducing the incidence of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
- Roflumilast should not be used to treat acute bronchospasm, as it has modest effects on FEV_1, is not a bronchodilator, and instead has anti-inflammatory actions. Combining roflumilast with a long-acting bronchodilator [salmeterol (Serevent) or tiotropium] results in improvements in FEV_1. The two trials used to obtain FDA approval reported roflumilast reduced COPD exacerbation rates by 15%–19% compared to placebo.
- For roflumilast, safety issues identified by the FDA included psychiatric events (including suicide), weight loss, GI upset and severe diarrhea, and nasal tumors. However, the FDA did not require additional prospective safety studies. A risk evaluation and mitigation strategy program was not required.

Relative Cost-Effectiveness Analysis, Relative Cost-Effectiveness Conclusion, UF Recommendation, BCF Recommendation—The P&T Committee reviewed proposed

condition sets for contract solicitation. The cost-effectiveness analysis and UF and BCF recommendations will be presented at an upcoming meeting.

C. Oral Anticoagulants

Background and Relative Clinical Effectiveness—The Oral Anticoagulant Drug Class is comprised of warfarin (Coumadin, generic), and the newer oral anticoagulants (NOACs) dabigatran (Pradaxa) and rivaroxaban (Xarelto). Another NOAC, apixaban (Eliquis) was approved in December 2012, and will be evaluated as a new drug at an upcoming meeting. Warfarin has been designated a BCF drug since before 1998, prior to implementation of the Uniform Formulary Rule in 2005.

Dabigatran, rivaroxaban, and apixaban are approved for stroke prevention in patients with non-valvular atrial fibrillation (Afib). Rivaroxaban has additional indications for prophylaxis of venous thromboembolism (VTE) in patients following hip or knee replacement surgery, and is also indicated to prevent recurrent VTE in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE).

A PORT analysis showed that MHS users of dabigatran have a mean age of 76 years and 91% of patients have an ICD-9 diagnosis code for Afib. MHS users of rivaroxaban have a mean age of 70 years and 41% of patients have an ICD-9 diagnosis code for Afib versus 39% of patients with a diagnosis code for hip of knee replacement surgery.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- The NOACs dabigatran and rivaroxaban have advantages of predictable anticoagulant effect, fixed dosing, and fewer drug interactions compared to warfarin (Coumadin, generic). Advantages of warfarin include its long history of use, reliable reversal agent (vitamin K), and adverse effects that are predictable and manageable.
- The NOACs offer a convenience to patients; laboratory monitoring for efficacy and dietary restrictions are not required. More data is needed in patients with renal and hepatic impairment. No reversal agent is available with the NOACs.
- In non-valvular Afib, dabigatran and apixaban were superior to poorly controlled warfarin (time in therapeutic range < 65.5%) at preventing stroke and systemic embolism, including hemorrhagic stroke; rivaroxaban was non-inferior to poorly controlled warfarin for these outcomes. Intracranial bleeding was lower with dabigatran, rivaroxaban, and apixaban compared to warfarin.
- For VTE prevention following orthopedic surgery, rivaroxaban was superior to enoxaparin at preventing symptomatic DVT, but at the cost of increased bleeding. Dabigatran and apixaban were similar to enoxaparin at VTE

prevention; no difference in bleeding was noticed with dabigatran, but a lower risk of bleeding was shown with apixaban versus enoxaparin.

- For prevention of VTE recurrence following DVT or PE, rivaroxaban in two trials was non-inferior to enoxaparin/warfarin for preventing recurrent VTE, with no difference in bleeding, and was superior to placebo in one trial for extended therapy. Dabigatran in one trial was non-inferior to enoxaparin/warfarin for preventing recurrent VTE, with no difference in bleeding. Apixaban was superior to placebo for prevention of recurrent VTE over 12 months (extended therapy) in one trial.
- Due to a lack of head-to-head trials, there is insufficient evidence to determine if one NOAC has advantages over the others for stroke prevention in non-valvular Afib, prophylaxis of VTE following hip or knee replacement surgery, or for prevention of VTE recurrence following DVT or PE.
- Patients require education and clinical monitoring to ensure appropriate use and avoid adverse reactions with the NOACs. Bleeding is a concern with all the NOACs, and dabigatran is associated with dyspepsia and major GI bleeding. For warfarin, a high risk of falls is not associated with risk of subsequent major bleeding.
- It remains to be determined whether the NOACs will increase the numbers of patients currently undertreated for stroke prevention in Afib. Also unknown is whether NOACs will improve persistence rates for anticoagulation therapy.

Relative Cost-Effectiveness Analysis and Conclusion—The P&T Committee evaluated the relative cost-effectiveness of the anticoagulant agents for stroke prevention in non-valvular Afib and for prophylaxis of VTE in patients undergoing knee or hip replacement surgery. CMAs were performed for both indications. Additionally, a cost-effectiveness analysis (CEA) evaluated the agents for stroke prevention in Afib.

- For the anticoagulant drugs, CMAs were used to compare the anticoagulant drug costs including relevant drug monitoring costs (e.g., international normalized ratio testing for warfarin and office visits).
- The CEA model was constructed based on comparisons of relevant clinical trial data from systematic reviews. The CEA model assessed the potential impact of anticoagulant treatment on the occurrence of stroke, bleeding, MI, and mortality. Results were reported as an incremental cost-effectiveness ratio (ICER) comparing the additional costs per life year gained with the NOACs dabigatran (Pradaxa) and rivaroxaban (Xarelto) in relation to warfarin.
- For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted. BIA results were presented to

the P&T Committee. The MHS projected budgetary impact varied depending on which medication was selected for BCF, UF, or NF status.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 against, 0 abstained, 0 absent) the following:

- Anticoagulant agents for stroke prevention in non-valvular AFib—CMA results showed that, in all scenarios, warfarin (Coumadin, generic), including drug monitoring costs, was the least costly agent. CEA results showed that the ICERs per life year gained with dabigatran and rivaroxaban in relation to warfarin were in a range that could be considered cost-effective to the MHS.
- Anticoagulant agents for DVT/PE prophylaxis in hip and knee replacement surgery—CMA results demonstrated that rivaroxaban (Xarelto) was a cost-effective alternative compared to enoxaparin (Lovenox), based on analysis of the average weighted price per day of therapy at all three POS.
- BIA results—Scenarios where all drugs remain on the UF resulted in the greatest cost-avoidance to the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) warfarin (Coumadin, generic), dabigatran (Pradaxa), and rivaroxaban (Xarelto) remain formulary on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) maintaining warfarin (Coumadin, generic) on the BCF. MTFs are highly encouraged to purchase the contracted warfarin generic product.

VI. UTILIZATION MANAGEMENT

A. PAs

1. **Tretinoin Age Limits**—The P&T Committee reviewed the current age limits for tretinoin, which does not allow use in patients older than 35 years. While treatment for acne is covered by TRICARE benefits, cosmetic services and supplies are excluded from the benefit, including treatments for photoaging of the skin.

a) ***COMMITTEE ACTION: TRETINOIN AGE LIMITS***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) removing the age limit for tretinoin products that are not exclusively labeled for cosmetic use at all 3 MHS POS (MTF, Mail Order, and the Retail Network). Acne can occur beyond age 35 years. Treatment for acne is covered by TRICARE benefits and low-cost tretinoin generic formulations are available. Tretinoin products/derivatives specifically indicated for cosmetic use as a result of the aging process (e.g., Renova, Refissa, Avage) remain excluded from the Pharmacy benefit.

2. **Zolpidem Gender-Based Dosing**—The P&T Committee discussed whether PA criteria are needed for zolpidem products, given new recommendations from the FDA in January 2013 regarding dosing in women. For women, lower dosing is recommended, as blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. A review of MHS prescriptions in the last six months of 2012 showed significant use of the higher zolpidem dosages in women.

   a) ***COMMITTEE ACTION: ZOLPIDEM GENDER-BASED DOSING*** The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) to not institute gender-based dosing PA criteria for zolpidem products, and to instead educate providers of the new recommendations, and notify patients via beneficiary newsletters of the concerns regarding impaired driving and activities requiring mental alertness the morning after use. The P&T Committee recommended re-evaluating this issue in six months to review MHS prescribing trends and whether additional measures are necessary.

B. Quantity Limits (QLs)

1. The P&T Committee reviewed quantity limit proposals for four products: aclidinium oral inhaler (Tudorza) for COPD, beclomethasone dipropionate nasal inhaler (Qnasl) for seasonal and perennial allergic rhinitis, ponatinib (Iclusig) tablets for treatment of patients with chronic myelogenous leukemia (CML), and cabozantinib (Cometriq) for patients with progressive, metastatic medullary thyroid cancer. QLs are recommended due to either existing QLs in the class to prevent wastage (inhalers) or due to high cost/adverse event profiles with subsequent need for dosage changes.

a) ***COMMITTEE ACTION: ACLIDINIUM (TUDORZA), BECLOMETHASONE (QNASAL) PONATINIB (ICLUSIG) and CABOZANTINIB (COMETRIQ) QLs***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) QLs for aclidinium oral inhaler (Tudorza), beclomethasone dipropionate nasal inhaler (Qnasl), ponatinib tablets (Iclusig), and cabozantinib (Cometriq), based on FDA-approved labeling. (See Appendix D.)

VII. ITEMS FOR INFORMATION

A. Options for Future DoD P&T Committee Meetings—Given the current budget restrictions regarding travel, the P&T Committee discussed options for future meetings, including Defense Connect Online (DCO) web conferences. Items of concern voiced by the P&T Committee if DCO teleconferences were implemented in lieu of in-person meetings included maintaining confidentiality of the contracted pricing solicitations, likelihood of interruption/inattention, decreased engagement by P&T Committee members, and potential lost opportunities for cost-avoidance, which would ultimately negatively impact TRICARE beneficiaries.

B. Cost-Effectiveness Modeling Review—The P&T Committee reviewed an analysis of previous UF economic evaluations that compared the performance of cost modeling projections and budget impact analyses to actual observed costs in the MHS. Overall, the evaluated cost-effectiveness models performed suitably, demonstrating expenditure and utilization trends that were similar between modeled outcomes and actual results. Possible factors contributing to variance between the modeled outcomes and actual results were discussed. Potential improvements identified during the review will be incorporated into future cost modeling scenarios and processes.

C. Smoking Cessation Program Final Rule—As of the meeting date, the Smoking Cessation Final Rule has not yet been published in the Code of Federal Regulations. The Proposed Rule provides that smoking cessation pharmaceutical agents, including FDA-approved over-the-counter pharmaceutical agents, will be available through the TRICARE Mail Order Pharmacy or the MTF. Until publication of the Final Rule, all UF/BCF recommendations for smoking cessation products from the May 2012 DoD P&T Committee meeting remain on hold.

D. POS Analysis Update—The PORT provided an update on MHS prescribing trends by point of service. The results showed that for branded medications considered maintenance products (e.g., used for chronic conditions and not specialty

medications), drug costs (30-day equivalent prescriptions) would have been about 27%–31% lower, if all prescriptions that were filled and dispensed in the Retail Network had instead been dispensed at the MTFs or at the Mail Order. In contrast, drug costs would have been about 13%–18% higher if generic drugs dispensed in the Retail Network had instead been dispensed in the MTFs or Mail Order.

E. **New TRICARE Pharmacy Copayments**—The P&T Committee was briefed on new pharmacy co-pays that were implemented in February 2013. At the Mail Order POS, co-pays for Tier 1 drugs (generics) remain $0, with co-pays of $13 for Tier 2 products (preferred brands) and $43 for Tier 3 products (non-preferred brands). The new co-pays in the Retail Network are $5 (Tier 1), $17 (Tier 2) and $44 (Tier 3). In the Mail Order, one co-pay applies for up to a 90-day supply, and one co-pay applies for up to a 30-day supply in the Retail Network.

F. **Step Therapy Safety Net**—The P&T Committee was briefed on the Rapid Response Step Therapy "Safety Net" Program implemented in September 2012. The program was initiated to educate beneficiaries affected by a step therapy reject and to educate providers regarding step-preferred drugs. The program targets beneficiaries who have not received a prescription fill for either a step-preferred or non step-preferred drug, after the initial reject. Since implementation, the MHS successful cases averaged 38.30%, which is similar to successful cases reported in commercial programs. Updates on the program will be periodically provided to the the P&T Committee.

VIII. ADJOURNMENT

The meeting adjourned at 1145 hours on February 21, 2013. The next meeting will be in May 2013.

Appendix A—Attendance: February 2013 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Quantity Limits

Appendix E—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix F—Table of Abbreviations

Appendix A—Attendance: February 2013 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Peter Bulatao, MS for COL John Spain, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
COL Ted Cieslak, MC	Army, Physician at Large
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CDR Brian King, MC for CAPT Walter Downs, MC	Navy, Internal Medicine Physician
LTC Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
COL Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Jeremy King, MC	Air Force, OB/GYN Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
COL Todd Williams, MS	Defense Medical Materiel Program Office
CDR Jay Peloquin, MSC via DCO	Defense Logistics Agency Troop Support
Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
CDR Matthew Baker, USPHS	Indian Health Service

Appendix A—Attendance (continued)

Guests	
Stephani Folts	Student, University of Incarnate Word Feik School of Pharmacy
Brian Hettler	Student, University of Incarnate Word Feik School of Pharmacy
Others Present	
LTC Chris Conrad, MS	DoD Pharmacoeconomic Center
LCDR Marisol Martinez, USPHS	DoD Pharmacoeconomic Center
LCDR Joshua Devine, USPHS	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
Lt Col Melinda Henne, MC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Linh Quach, MSC	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Amy Lugo via DCO	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe via DCO	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
LT Kendra Jenkins, USPHS	Pharmacy Resident
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Mr. Kirk Stocker	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Zolpidem sublingual low dose (Intermezzo) **Newer Sedative Hypnotic-1 (SED-1s)**	• No alternative formulary agent – patient has swallowing difficulties and requires a product for middle-of-the-night awakening.
• Diclofenac 1.5% solution (Pennsaid) **Topical Pain Medications**	• Patient has experienced significant adverse effects from ALL of the formulary medications that are not expected to occur with the nonformulary topical pain medication (e.g., patient had intolerable dry skin with use of diclofenac gel and has gastrointestinal or cardiovascular risk factors that preclude use of oral NSAIDs). • Formulary agents result or are likely to result in therapeutic failure (e.g., patient had intolerable dry skin with use of diclofenac gel and has gastrointestinal or cardiovascular risk factors that preclude use of oral NSAIDs). • No alternative formulary agent – patient requires topical agent with dimethyl sulfoxide (DMSO) to aid in skin absorption.
• Diclofenac 1.3% patch (Flector) **Topical Pain Medications**	• Patient has experienced significant adverse effects from ALL of the formulary medications that are not expected to occur with the nonformulary topical pain medication (e.g., patient experienced intolerable dry skin with use of diclofenac gel and has gastrointestinal or cardiovascular risk factors that preclude use of oral NSAIDs). • No alternative formulary agent – patient requires use of patch for treatment of pain associated with acute strain/sprain and cannot use oral NSAIDs or diclofenac gel products.

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
▪ Zolpidem sublingual low dose (Intermezzo) **Newer Sedative Hypnotics-1 (SED-1s)**	A trial of generic zolpidem IR or zaleplon is required for new users of Intermezzo. Automated PA criteria – The patient has filled a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days. Manual PA criteria – The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.
▪ Lidocaine 5% patch (Lidoderm) **Topical Pain Medications**	New and current users of Lidoderm are required to undergo the PA process. Manual PA criteria Lidoderm is approved if: – The patient has a diagnosis of postherpetic neuropathy – The patient has a diagnosis of another form of peripheral neuropathy – The patient has a diagnosis of other pain (non-neuropathic) and an occupational or clinical reason exists and other analgesics are contraindicated • Coverage for other uses of Lidoderm is not approved.

Appendix D—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
• aclidinium oral inhaler (Tudorza) **Pulmonary Disease II Drugs – Long-Acting Muscarinic Agent**	• Retail: 1 inhalers/30 days • Mail Order and MTF: 3 inhalers/90 days
• beclomethasone dipropionate aerosol nasal inhaler (Qnasl) **Nasal Allergy Drugs**	• Retail: 1 inhalers/30 days • Mail Order and MTF: 3 inhalers/90 days
• ponatinib (Iclusig) **Oral Chemotherapy Agents for chronic myelogenous leukemia**	• 15 mg tablets: – Retail: 90 tabs/30 days – Mail Order and MTF: 135 tabs/45 days • 45 mg tablets: – Retail: 30 tabs/30 days – Mail order and MTF: 45 tabs/45 days
• cabozantinib (Cometriq) **Oral Chemotherapy Agents for metastatic medullary thyroid cancer**	• 140, 100 and 60 mg daily dose cartons – Retail: 4 packs/30 days – Mail Order: 8 packs /45 days

Appendix E—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2013	**Topical Pain Medications**	UF Class Review	None	▪ Lidocaine 5% patch (Lidoderm) ▪ Diclofenac 1% gel (Voltaren)	▪ Diclofenac 1.3% patch (Flector) ▪ Diclofenac 1.5% solution (Pennsaid)	Pending signing of the minutes/ 90 days	PA applies	PA for Lidoderm applies to new and current users (see Appendix C)
Feb 2013	**Oral Anticoagulants**	UF Class review	Warfarin	▪ Dabigatran (Pradaxa) ▪ Rivaroxaban (Xarelto)	▪ N/A (no drugs designated nonformulary	Pending signing of the minutes	-	-
Feb 2013	**Newer Sedative Hypnotics-1 (SED-1s)**	New Drug	Zolpidem IR	▪ Zolpidem ER ▪ Eszopiclone (Lunesta) ▪ Doxepin (Silenor) ▪ Zaleplon	▪ **Zolpidem sublingual low dose (Intermezzo) recommended for NF placement Feb 2013** ▪ Rozerem (Ramelteon) ▪ Zolpidem sublingual (Edluar)	Pending signing of the minutes/ 60 days	PA applies	Step therapy (Automated PA); requires trial of zolpidem IR or zaleplon before any other SED-1

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix F—Table of Abbreviations

Afib	atrial fibrillation
ASD(HA)	Assistant Secretary of Defense for Health Affairs
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CFC	chlorofluorocarbon
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DCO	Defense Connect Online
DoD	Department of Defense
DMSO	dimethyl sulfoxide
DPI	dry powder inhaler
DVT	deep vein thrombosis
ER	extended release
FDA	U.S. Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GI	gastrointestinal
ICER	incremental cost-effectiveness ratio
IR	immediate release
MI	myocardial infarction
MDI	metered dose inhaler
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NAOCs	newer oral anticoagulants
NF	nonformulary
NSAIDs	nonsteroidal anti-inflammatory drugs
P&T	Pharmacy and Therapeutics
PA	prior authorization
PE	pulmonary embolism
PEC	Pharmacoeconomic Center
PHN	postherpetic neuralgia
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
SED-1s	newer sedative hypnotic-1 agents
LAMA	long-acting muscarinic agent
SAMA	short-acting muscarinic agent
SL	sublingual
UF	Uniform Formulary
VTE	venous thromboembolism

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2012

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. High Potency Narcotic Analgesics—Oxycodone Immediate Release (IR) (Oxecta)*Relative Clinical Effectiveness Conclusion*—The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Oxecta is the first abuse deterrent IR oxycodone formulation marketed. There is no evidence to suggest oxycodone IR (Oxecta) has a compelling clinical advantage over the other high potency narcotic analgesics included on the Uniform Formulary (UF).

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that oxycodone IR (Oxecta) was not cost-effective when compared to other high potency narcotic analgesics included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) oxycodone IR (Oxecta) be designated nonformulary (NF) due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***
The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) MN criteria for Oxecta: there are no formulary alternatives and the patient requires a tamper resistant formulation of oxycodone IR.

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS), and TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April 17, 2013.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

II. UNIFORM FORMULARY DRUG CLASS REVIEWS

A. Non-Insulin Diabetes Drugs—Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)

Relative Clinical Effectiveness Conclusion—Step therapy implemented in April 2011 requires that new GLP1RA users try metformin or sulfonylurea first, and that new GLP1RA users try exenatide twice daily (BID) (Byetta) before TRICARE® will cover the other agents in this drug subclass. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Exenatide BID injection (Byetta), liraglutide once daily injection (Victoza), and exenatide once weekly injection (Bydureon) all decrease hemoglobin A1c ~ 1%–2% from baseline when used as monotherapy or in combination with other oral agents.
- When compared head-to-head, overall there are no clinically relevant differences between the three GLP1RAs with regard to effect on glycemic control.
- Bydureon offers additional patient convenience given its once weekly dosing regimen and does not require titration compared to Byetta, but is not available in a pre-filled syringe.
- There are no studies evaluating adherence with the three GLP1RAs.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that exenatide BID (Byetta) was the most cost-effective GLP1RA, based on the weighted average cost per day of treatment across all three POS, followed by exenatide once weekly (Bydureon) and liraglutide (Victoza). Results from the cost minimization and budget impact analyses showed scenarios where exenatide BID (Byetta), exenatide once weekly (Bydureon) and liraglutide (Victoza) are all designated UF presented a cost avoidance projection comparable to the current UF scenario where all GLP1RAs are UF. Data was not available to assess the potential pharmacoeconomic impact of longer-acting GLP1RA formulations on medication adherence and health-related outcomes in this cost-effectiveness evaluation.

1. ***COMMITTEE ACTION: UF/BASIC CORE FORMULARY (BCF) RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:

- Designating exenatide BID (Byetta), liraglutide once daily (Victoza), and exenatide once weekly (Bydureon) as formulary on the UF;
- Excluding Byetta, Victoza, and Bydureon GLP1RAs from the BCF; and,
- Removing the current requirement for a trial of Byetta prior to the other GLP1RAs (removing the subclass step therapy requirement). As a result, there would no longer be a preferred GLP1RA product.

2. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining the current PA requiring a trial of metformin or a sulfonylurea prior to the use of exenatide BID (Byetta), liraglutide once daily (Victoza), or exenatide once weekly (Bydureon). A trial of metformin or a sulfonylurea would not be required for patients with an adverse event, contraindication to, or inadequate response with metformin or sulfonylurea. Use of a GLP1RA product is approved only for patients with type 2 diabetes mellitus. Automated PA criteria (step-therapy) and manual PA criteria remain the same as recommended at the November 2010 P&T Committee meeting, and implemented in April 2011. (See Appendix C for full criteria.)

3. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 30-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is March 20, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Overactive Bladder Drugs (OABs)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Review of the clinical literature for efficacy, safety, and tolerability data since the last P&T Committee review in 2008 did not add substantial new information.
- Persistence rates within the Military Health System (MHS) remain low at 12% for all the OAB drugs. As needed use of the OAB drugs is 26% in the MHS.

- There are no studies evaluating clinical outcomes, such as reduced fall risk or delayed nursing home placement with the OAB drugs.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 against, 0 abstained, 0 absent) that for preferred formulary placement status, oxybutynin IR (Ditropan, generics) was the least costly agent based on the weighted average cost per day of treatment across all three POS, followed by oxybutynin ER (Ditropan XL, generics), tolterodine ER (Detrol LA), solifenacin (Vesicare), oxybutynin 10% gel (Gelnique), fesoterodine (Toviaz), oxybutynin transdermal delivery system (Oxytrol), trospium IR (Sanctura, generics), trospium ER (Sanctura XR, generics), darifenacin (Enablex), and tolterodine IR (Detrol, generics).

Results from the cost minimization analysis (CMA) and budget impact analysis (BIA) showed that among available formulary options examined, the scenario where oxybutynin IR, oxybutynin ER, and Detrol LA were designated as step-preferred, with step therapy applied to all current and new users of non-preferred OAB products, was most cost-effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:
    - UF and step-preferred ("in front of the step"): tolterodine extended release (ER) (Detrol LA), oxybutynin IR (Ditropan, generics), and oxybutynin ER (Ditropan XL, generics). Prior authorization would require that all patients try Detrol LA, oxybutynin IR, or oxybutynin ER before TRICARE will cover the other agents in this drug class.
    - UF and non step-preferred ("behind the step"): trospium IR (Sanctura, generics), trospium ER (Sanctura XR, generics), tolterodine IR (Detrol, generics) and solifenacin (Vesicare)
        - When the generics to Sanctura, Sanctura XR, and Detrol become cost-effective relative to the step-preferred agents, the generics will become step-preferred without further action by the P&T Committee, Beneficiary Advisory Panel, or Director, TMA. A generic agent is cost-effective relative to step-preferred agents when the generic agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the step-preferred agent.
    - NF and non step-preferred: darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin transdermal delivery system (Oxytrol), and oxybutynin 10% gel (Gelnique).

- Step therapy would apply to all users (current and new) of the OAB drugs.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining Detrol LA and oxybutynin ER on the BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) PA criteria for all current and new users of the OAB drugs, requiring a trial of Detrol LA, oxybutynin IR, or oxybutynin ER prior to the use of the other OAB drugs. A trial of the step-preferred OAB drugs would not be required in patients with an adverse event, inadequate response, or contraindication to Detrol LA, oxybutynin ER, or oxybutynin IR. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Enablex, Toviaz, Oxytrol, and Gelnique 10%. (See Appendix B for full MN criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is May 15, 2013.

Addendum to the UF recommendation: During a post meeting bid review, it was determined that after-step bids should not be accepted and modeled due to verbiage in the bid solicitation. As a result of this determination, the cost analysis was recalculated. This new cost model was presented to the DoD P&T committee via electronic means. An electronic vote was taken to determine a) whether to accept the new cost review, maintain the current scenario and maintain current UF recommendations, or b) withdraw the UF recommendation, rebid the class and present results at the Feb 2013 meeting.

6. ***COMMITTEE ACTION: ADDENDUM TO UF RECOMMENDATION***
The P&T Committee recommended (9 for, 5 opposed, 0 abstained, 3 absent) to approve the current scenario, which maintains the UF recommendation, step therapy requirements for all new and current users of OAB drugs, and PA criteria.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Gastrointestinal-2 Oral Antibiotic Drugs (GI-2)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- For hepatic encephalopathy (HE), rifaximin is superior to lactulose in improving symptoms. While rifaximin is approved for monotherapy, it is commonly used in combination with lactulose, and is better tolerated than lactulose.
- For *Clostridium difficile* infection (CDI):
  - Metronidazole is equally effective as vancomycin in treating mild to moderate CDI, but for severe CDI vancomycin results in higher clinical cure rates.
  - Fidaxomicin and vancomycin provide similar clinical cure rates for CDI; however, fidaxomicin decreases recurrence and increases global cure rates to a greater extent than vancomycin.
  - Comparative efficacy for nitazoxanide and rifaximin for CDI cannot be assessed, given the small numbers of trials.
- For travelers' diarrhea (TD), practice guidelines and a systematic review recommend fluoroquinolones (e.g., levofloxacin, ciprofloxacin) as first line treatment. Rifaximin is FDA-approved for TD but is limited to TD caused by noninvasive strains of *Escherichia coli*.
- Rifaximin is not FDA-approved for irritable bowel syndrome (IBS), and there is insufficient evidence to support its use for IBS. Other non-supportable uses of rifaximin include inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, rosacea, and any other non FDA-approved indication.

Relative Cost-Effectiveness Conclusion—Pharmacoeconomic analyses, including CMA, were performed for the GI-2 Drug Class. Cost analyses were based on the disease states discussed in the clinical section. Comparative costs for agents from other drug classes were considered (e.g., lactulose, fluoroquinolones), due to the conclusions from the clinical effectiveness review. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following: for HE, lactulose was the least costly agent, followed by lactulose in combination with neomycin, and then rifaximin (Xifaxan). For CDI, metronidazole was the least costly agent, followed by vancomycin, with

fidaxomicin (Dificid) as the most costly agent. For TD, ciprofloxacin was the least costly agent followed by rifaximin (Xifaxan) and nitazoxanide (Alinia).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 2 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS.
    - UF: metronidazole, vancomycin, neomycin, rifaximin (Xifaxan), nitazoxanide (Alinia), and fidaxomicin (Dificid)
    - Fidaxomicin (Dificid) is available solely in the retail network. Availability of Dificid from mail order is not recommended due to the time constraints for treating acute *C. difficile* infection. Additionally, due to noncompliance with the Trade Agreements Act, Dificid is excluded from mail order and military treatment facilities (MTFs). Efforts to allow availability of Dificid at the MTFs are ongoing at this time.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining metronidazole 250 mg and 500 mg tablets on the BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) PA criteria for rifaximin (Xifaxan) 200 mg for TD. Automated PA criteria would require use of a fluoroquinolone prior to use of rifaximin 200 mg for travelers' diarrhea, unless the patient is under age 18, has a documented allergy to a fluoroquinolone, or is returning from an area with high fluoroquinolone resistance. The P&T Committee also recommended (14 for, 2 opposed, 1 abstained, 0 absent) PA criteria for rifaximin (Xifaxan) 550 mg for hepatic encephalopathy, consistent with the FDA-approved labeling. Other uses of rifaximin are not covered, including *C. difficile* infection, irritable bowel syndrome, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, and rosacea. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) QLs for the following GI-2 drugs:
    - Fidaxomicin (Dificid): 20 tablets with no refill in all POS, consistent with the product labeling
    - Rifaximin (Xifaxan) 200 mg: For travelers' diarrhea, if prior authorization is approved, a 3-day supply (9 tablets) in all three POS is

recommended, consistent with the product labeling. For hepatic encephalopathy, if prior authorization is approved, overrides will be allowed.

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS. Based in the P&T Committee's recommendation, the effective date is May 15, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Hepatitis C Drugs*Relative Clinical Effectiveness Conclusion*—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Triple therapy with a direct acting antiviral agent (boceprevir or telaprevir), PEG-interferon, and ribavirin increases sustained viral response (SVR) rates to a greater extent than dual therapy with PEG-interferon and ribavirin (PR).
- There is insufficient evidence to conclude whether boceprevir (Victrelis) or telaprevir (Incivek) is superior to the other, due to the lack of direct comparative trials. Telaprevir offers patient convenience due to its shorter treatment course than boceprevir (12 weeks versus 44 weeks), but this has not resulted in higher SVR rates.
- There is insufficient evidence to support a preference of Pegasys over PEG-Intron, but there do not appear to be clinically relevant differences in efficacy.
- Response-guided therapy for clinically appropriate patient populations maintains high levels of efficacy while shortening drug exposure times and treatment course duration.
- Compared with PR dual therapy, boceprevir triple therapy increases the risk for anemia and telaprevir triple therapy increases the risk for anemia and rash.

Relative Cost-Effectiveness Conclusion—CMA results of the direct acting antiviral agents (DAAs) showed response-guided therapy could be less costly with boceprevir than with telaprevir, based on current dosing recommendations. However, when each

agent was taken over its full treatment duration, telaprevir was less costly than boceprevir. The cost-effectiveness analysis concluded that combination use of DAAs plus PEG-interferon alfa and ribavirin was a cost-effective option for the treatment of chronic hepatitis C. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that the most cost-effective scenario placed ribavirin (generics), PEG-interferon alfa-2a (Pegasys), interferon alfa-2b (Intron A), PEG-interferon alfa-2b (PEG-Intron), boceprevir (Victrelis), and telaprevir (Incivek) as formulary on the UF, and ribavirin (Ribapak) and interferon alfacon-1 (Infergen) as NF on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:
    - UF status for boceprevir (Victrelis), telaprevir (Incivek), PEG-interferon alfa-2a (Pegasys), PEG-interferon alfa-2b (PEG-Intron), interferon alfa-2b (Intron A), and ribavirin (except for the Ribapak formulation); and,
    - NF status for interferon alfacon-1 (Infergen) and the ribavirin Ribapak formulation, due to the lack of compelling clinical advantages and cost disadvantages when compared to the UF products.

2. ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) designating telaprevir (Incivek), PEG-interferon alfa-2a (Pegasys), and ribavirin 200 mg capsules (generics) as ECF products, based on clinical and cost-effectiveness.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for boceprevir (Victrelis) and telaprevir (Incivek), consistent with the FDA-approved labeling. Prior authorization will expire after 12 weeks for telaprevir and 44 weeks for boceprevir. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following QLs:
    - For boceprevir and telaprevir: a 28-day supply per prescription at all three POS, with no multiple fills for multiple co-pays; and,
    - For all the interferon and ribavirin products: a 90-day supply in MTFs and Mail Order, and a 30-day supply in the retail network.

5. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for

interferon alfacon-1 (Infergen) and Ribapak. (See Appendix B for full MN criteria.)

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April 17, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

III. RE-EVALUATION OF NF AGENTS

On an ongoing basis, the DoD Pharmacoeconomic Center monitors changes in the clinical information, current costs, and utilization trends to determine whether the UF status of agents designated as NF needs to be readdressed. The P&T Committee's process for the re-evaluation of NF agents established at the May 2007 meeting was approved by the Director, TMA on June 24, 2007, and is outlined in Appendix E.

The P&T Committee reevaluated the UF status of Lexapro (escitalopram) and pantoprazole (Protonix) in light of recent price reductions in the generic formulations across all three POS.

1. ***COMMITTEE ACTION: ESCITALOPRAM UF RECOMMENDATION AND IMPLEMENTATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) reclassification of escitalopram (Lexapro, generic) as formulary on the UF, as cost-effective generic formulations are now available in all three POS. Implementation will occur upon signing of the minutes.

2. ***COMMITTEE ACTION: PANTOPRAZOLE UF RECOMMENDATION AND IMPLEMENTATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) reclassification of pantoprazole (Protonix, generic) as formulary on the UF, as cost-effective generic formulations are now available in all three POS. Implementation will occur upon signing of the minutes.

Director, TMA, Decision: ☒ Approved □ Disapproved

Approved, but modified as follows:

IV. UTILIZATION MANAGEMENT

A. PAs

1. **Phosphodiesterase-5 (PDE-5) Inhibitors**—The PA criteria for the PDE-5 Inhibitor Drug Class was reviewed. Prior authorization allows use of a PDE-5 inhibitor following prostatectomy for preservation/restoration of erectile function for one year. There is no published evidence suggesting benefit if the PDE-5 inhibitor is initiated beyond one year after surgery. Recommendations were to clarify the existing PA criteria to state that prostatectomy surgery must have occurred less than 365 days from the date the PA form is signed.

   The additional recommendations were:

   - For Cialis: that existing criteria that apply to patients with benign prostatic hyperplasia (BPH) also apply to patients with BPH and erectile dysfunction (ED); and,
   - For sildenafil used for primary pulmonary hypertension (PPH): that the sildenafil dosage formulation specifically state 20 mg tablets to discourage use of sildenafil 20 mg tablets for ED.

   a) ***COMMITTEE ACTION: PDE-5 INHIBITOR PA CRITERIA***
   The P&T Committee recommended (14 for, 1 opposed, 2 abstained, 0 absent) PA criteria for the PDE-5 inhibitors (1) clarifying the existing PA criteria to state that prostatectomy surgery must have occurred less than 365 days from the date the PA form is signed; (2) for Cialis, that the existing criteria also apply to patients with BPH and ED; and, (3) for sildenafil for PPH, that the sildenafil dosage formulation will specifically state 20 mg tablets. (See Appendix C for full criteria.)

2. **Testosterone Replacement Therapy (TRT)**—PA criteria for the TRT Drug Class were developed at the August 2012 meeting and signed by the Director, TMA on November 8, 2012. The P&T Committee reviewed the PA criteria for use of TRT in women, which was based on level A evidence from the American College of Obstetrics and Gynecology, as outlined in a 2011 Clinical Bulletin. The Clinical Bulletin specifically mentions that

there is little evidence to support long-term TRT use (longer than 6 months) in women.

a) ***COMMITTEE ACTION: TRT USE IN WOMEN PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the PA criteria for use of TRT in women to limit use to six months. (See Appendix C for full criteria.)

3. **Injectable Gonadotropins**—PA criteria currently apply to the injectable gonadotropins (fertility agents). Injectable gonadotropins are not covered under the TRICARE pharmacy benefit if they are being used in conjunction with a noncoital reproductive technology. In 2010, the Assistant Secretary of Defense for Health Affairs (ASD(HA)) authorized in vitro fertilization services for the benefit of severely or seriously ill/injured active duty service members. Implementation guidance for these services was developed in an April 2012 ASD(HA) policy.

a) ***COMMITTEE ACTION: INJECTABLE GONADOTROPINS PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 2 abstained, 0 absent) revising the PA criteria for the injectable gonadotropins (fertility agents), to allow for use in conjunction with a noncoital reproductive technology, as outlined in the ASD(HA) April 2012 "Policy for Assisted Reproductive Services for the Benefit of Seriously or Severely Ill/Injured (Category II or III) Active Duty Service Members." A Signed Authorization Memorandum from TMA must be included with the prescription. (See Appendix C for full criteria.)

4. **Adalimumab (Humira)**—The FDA recently approved a new indication for Humira, the designated ECF agent in the targeted immunomodulatory biologics (TIBs) Drug Class. Humira is now indicated for the treatment of moderately to severely active ulcerative colitis following inadequate response to immunosuppressants such as corticosteroids, azathioprine, and 6-mercaptopurine.

a) ***COMMITTEE ACTION: ADALIMUMAB (HUMIRA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the existing PA criteria for Humira to incorporate the new indication for ulcerative colitis, consistent with the FDA-approved product labeling. (See Appendix C for full criteria.)

5. **Enzalutamide (Xtandi) and Abiratone (Zytiga)**—Two new drugs for metastatic castration-resistant prostate cancer were recently approved. Xtandi and Zytiga are costly agents with specific FDA-indications, requiring use of prior docetaxel-containing regimens.

    a) ***COMMITTEE ACTION: ENZALUTAMIDE (XTANDI) AND ABIRATONE (ZYTIGA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for enzalutamide (Xtandi), and abiratone (Zytiga), consistent with the FDA-approved product labeling. (See Appendix C for full criteria.)

B. QLs

1. **Ipratropium/albuterol (Combivent Respimat)**—Ipratropium/albuterol (Combivent Respimat) oral inhaler is a non chlorofluorocarbon-containing reformulation of ipratropium and albuterol. The current chlorofluorocarbon (CFC) formulation, Combivent, will be phased out and replaced by Combivent Respimat. Combivent supplies are to be exhausted by December 31, 2013. The entire chronic obstructive pulmonary disease drug class will be reviewed formally for UF placement, including the BCF, at an upcoming meeting. Quantity limits currently apply to all oral inhalers.

    a) ***COMMITTEE ACTION: IPRATROPIUM/ALBUTEROL (COMBIVENT RESPIMAT) QL***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) QLs for Combivent Respimat, restricting the maximum allowable quantity at the retail point of service to 2 inhalers in 30 days and 5 inhalers in 90 days at Mail Order and MTFs, consistent with recommended dosing. (See Appendix D.)

2. **Azelastine/fluticasone propionate (Dymista), adalimumab (Humira), enzalutamide (Xtandi), and abiratone (Zytiga)**—The P&T Committee evaluated QLs for several other drugs, including azelastine/fluticasone propionate nasal inhaler (Dymista) (Nasal Allergy Drug Class), Humira for the new indication ulcerative colitis (TIBs Drug Class), and Xtandi and Zytiga (oral chemotherapy drugs for prostate cancer).

    a) ***COMMITTEE ACTION: DYMISTA, HUMIRA, XTANDI, AND ZYTIGA QL***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) QLs for Dymista, Humira for ulcerative colitis, Xtandi, and Zytiga, as outlined in Appendix D, consistent with FDA-approved product labeling.

Director, TMA, Decision: ☒ Approved □ Disapproved

Approved, but modified as follows:

V. SECTION 703

A. Section 703—The P&T Committee reviewed Kaon (branded potassium gluconate) and Pamine (branded methscopolamine) to determine MN and pre-authorization criteria. These two products were identified as not fulfilling refund requirements required in section 703 of the 2008 National Defense Authorization Act. These drugs were designated NF on the UF at previous P&T Committee meetings.

1. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following should apply to Kaon and Pamine. Coverage at retail network pharmacies would be approved if the patient met all of the following criteria:

   a) Manual Pre-Authorization Criteria:

      (1) Obtaining the product from home delivery would be detrimental to the patient.

      (2) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

   b) Implementation will occur upon signing of the minutes.

   The pre-authorization criteria listed above do not apply to any point of service other than retail network pharmacies.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. OVERVIEWS

Two drug class overviews were presented to the P&T Committee, the oral anticoagulants (vitamin K antagonists, direct thrombin inhibitors, Factor Xa inhibitors), and the drugs for chronic obstructive pulmonary disease (COPD). Neither drug class has previously been reviewed for UF status. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

VII. ITEMS FOR INFORMATION

A. Joint Forces Pharmacy Seminar (JFPS) Presentation—The P&T Committee was briefed on spends and trends in MHS drug utilization, which was presented at the JFPS in October.

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

Feb 13, 2013
Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

November 2012

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on November 14 and 15, 2012, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Jonathon Woodson M.D., Director, approved the minutes for the August 2012 DoD P&T Committee meeting on November 8, 2012.
2. **Correction to the May 2012 Minutes**—The May minutes were corrected to state the quantity limits for the smoking cessation products, nicotine gum and nicotine lozenge, are limited to 600 pieces per 60-day claim, rounded to the nearest multiple of the package size (e.g., boxes of 75 or 100). The QL recommendations are contingent on publication of the Final Rule.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. High Potency Narcotic Analgesics—Oxycodone Immediate Release (IR) (Oxecta)

Relative Clinical Effectiveness—Oxecta is a formulation of oxycodone IR that is tamper resistant but not tamper proof. FDA approval was based on demonstrated bioequivalence to the Roxycodone proprietary formulation of oxycodone IR. One small

"drug liking" study showed a reduced "liking" for Oxecta versus Roxycodone, but the widespread clinical applicability of these results is unknown.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Oxecta is the first abuse deterrent IR oxycodone formulation marketed. There is no evidence to suggest oxycodone IR (Oxecta) has a compelling clinical advantage over the other high potency narcotic analgesics included on the UF.

Relative Cost-Effectiveness Analysis and Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per tablet at all three points of service (POS) was evaluated for oxycodone IR (Oxecta) in relation to the other drugs in the high potency narcotic subclass. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Oxecta was not cost-effective when compared to other high potency narcotics included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) oxycodone IR (Oxecta) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) MN criteria for Oxecta. (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS), and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April 17, 2013.

V. UF DRUG CLASS REVIEWS

A. Non-Insulin Diabetes Drugs—Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)

Background and Relative Clinical Effectiveness—The GLP1RAs are a subclass of the Non-Insulin Diabetes Drug Class, which is comprised of exenatide twice daily (BID) injection (Byetta), liraglutide once daily injection (Victoza), and exenatide once weekly injection (Bydureon). Bydureon is the newest entrant to the class.

The GLP1RA class was previously reviewed for UF placement in November 2010.

Step therapy implemented in April 2011 requires a trial of metformin or a sulfonylurea prior to use of a GLP1RA. An additional step therapy/prior authorization (PA) requirement has been in effect for the GLP1RAs subclass since April 2011, requiring that new GLP1RA users try exenatide BID (Byetta) before TRICARE® will cover the other agents in this drug subclass. The Pharmacy Outcomes Research Team (PORT) provided the P&T Committee detailed analyses of current MHS prescription patterns. The data presented were factored into the relative clinical and cost-effectiveness determinations.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- Metformin is the most cost-effective agent and remains the first line treatment in all patients with type 2 diabetes mellitus, unless contraindications exist, due to positive outcomes data from the United Kingdom Prospective Diabetes Study.
- When used as monotherapy or in combination with other oral agents, GLP1RAs decrease hemoglobin A1c approximately 1%–2% from baseline. When compared head-to-head, overall there are no clinically relevant differences between the three GLP1RAs with regard to effect on glycemic control.
- Bydureon and Victoza have a greater effect than Byetta on fasting blood glucose due to a longer duration of action. Byetta has a greater effect on post-prandial glucose than the other two GLP1RAs.
- Gastrointestinal issues are the most common adverse effect with the GLP1RAs. Bydureon has a lower incidence of nausea (14.4%) compared to Victoza (20.7%) or Byetta (34.7%). Injection site reactions are more common with Bydureon (17.1%) than Byetta (12.7%), insulin glargine (1.8%), or placebo (6.4%–13%).
- Bydureon offers additional patient convenience given its once weekly dosing regimen and does not require titration compared to Byetta, but is not available in a pre-filled syringe.
- There are no studies evaluating adherence with the three GLP1RAs.
- There are no published trials that assess long-term outcomes; however, the LEADER and EXSCEL studies evaluating long-term cardiovascular safety are currently ongoing.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses were performed for the GLP1RA subclass, including cost minimization analysis (CMA) and budget impact analysis (BIA). For the BIAs, several of the model's key

assumptions were varied, with corresponding sensitivity analyses conducted. Methods used for CMA and BIAs were based on current step therapy requiring a trial of metformin or a sulfonylurea prior to a patient receiving a GLP1RA.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that exenatide BID (Byetta) was the most cost-effective GLP1RA, based on the weighted average cost per day of treatment across all three POS, followed by exenatide once weekly (Bydureon) and liraglutide (Victoza) (ranked in order from most to least cost-effective). Results from the CMA and BIA showed scenarios where exenatide BID (Byetta), exenatide once weekly (Bydureon), and liraglutide (Victoza) are all designated UF presented a cost avoidance projection comparable (i.e., within a margin of error) to the current UF scenario where all GLP1RAs are UF. Data was not available to assess the potential pharmacoeconomic impact of longer-acting GLP1RA formulations on medication adherence and health-related outcomes in this cost-effectiveness evaluation.

1. ***COMMITTEE ACTION: UF/BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:

    - Designating exenatide BID (Byetta), liraglutide once daily (Victoza), and exenatide once weekly (Bydureon) as formulary on the UF;
    - Excluding Byetta, Victoza, and Bydureon GLP1RAs from the BCF; and,
    - Removing the current requirement for a trial of Byetta prior to the other GLP1RAs (removing the subclass step therapy requirement). As a result, there would no longer be a preferred GLP1RA product.

2. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining the current PA requiring a trial of metformin or a sulfonylurea prior to the use of exenatide BID (Byetta), liraglutide once daily (Victoza), or exenatide once weekly (Bydureon). A trial of metformin or a sulfonylurea would not be required for patients with an adverse event, contraindication to, or inadequate response with metformin or sulfonylurea. Use of a GLP1RA product is approved only for patients with type 2 diabetes mellitus. Automated PA criteria (step-therapy) and manual PA criteria remain the same as recommended at the November 2010 P&T Committee meeting, and implemented in April 2011. (See Appendix C for full criteria.)

3. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 30-day

implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is March 20, 2013.

B. Overactive Bladder Drugs (OABs)

Background and Relative Clinical Effectiveness—The Overactive Bladder (OAB) Drug Class is comprised of darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin IR (Ditropan, generics), oxybutynin extended release (ER) (Ditropan XL, generics), oxybutynin transdermal delivery system (TDS) (Oxytrol), oxybutynin 10% gel (Gelnique), solifenacin (Vesicare), tolterodine IR (Detrol, generics), tolterodine ER (Detrol LA), trospium IR (Sanctura, generics), and trospium ER (Sanctura XR, generics). Generic formulations of Detrol IR, Sanctura IR and Sanctura XR recently entered the market. The OAB drug class has been previously reviewed for UF placement in August 2008, and May and November 2009.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- Review of the clinical literature for efficacy, safety, and tolerability data since the last P&T Committee review in 2008 did not add substantial new information.
- The OAB agents are statistically superior to placebo, but the placebo response rates are high for the class, ranging from 30% to 50%.
- There is insufficient evidence to suggest whether one OAB drug is superior to another. Small studies of low quality evidence reported fesoterodine (Toviaz) was statistically superior to tolterodine, and solifenacin (Vesicare) was statistically superior to tolterodine, but the clinical effect is small, relating to a reduction in urge episodes/incontinent episodes of approximately one episode/day.
- No OAB agent has a superior safety profile. Oxybutynin TDS (Oxytrol) causes less dry mouth than tolterodine ER, but has higher withdrawal rates. There is scant safety data for the oxybutynin 10% gel (Gelnique) formulation, but the effects are likely to be similar to oxybutynin TDS with regards to dry mouth.
- Overall, adverse drug effects are lower with the ER formulations than IR formulations. The newer agents do not have significantly lower incidence of dry mouth or constipation than the older OAB drugs.
- Persistence rates within the MHS remain low at 12% for all the OAB drugs. As needed use of the OAB drugs is 26% in the MHS.
- There are no studies evaluating clinical outcomes, such as reduced fall risk or delayed nursing home placement with the OAB drugs.
- There is a high degree of therapeutic interchangeability within the class.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses were performed for the OABs, including CMA and BIA. For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted. The P&T Committee concluded (17 for, 0 against, 0 abstained, 0 absent) that for preferred formulary placement status, oxybutynin IR (Ditropan, generics) was the least costly agent based on the weighted average cost per day of treatment across all three POS, followed by oxybutynin ER (Ditropan XL, generics), tolterodine ER (Detrol LA), solifenacin (Vesicare), oxybutynin 10% gel (Gelnique), fesoterodine (Toviaz), oxybutynin TDS (Oxytrol), trospium IR (Sanctura, generics), trospium ER (Sanctura XR, generics), darifenacin (Enablex), and tolterodine IR (Detrol, generics).

BIA results were presented to the P&T Committee and indicated that step therapy scenarios were more cost-effective compared to the current baseline (non step therapy). The MHS projected budgetary impact varied depending on which medication was selected for step-preferred status. CMA and BIA results showed that among available formulary options examined, the scenario where oxybutynin IR, oxybutynin ER, and Detrol LA were designated as step-preferred, with step therapy applied to all current and new users of non-preferred OAB products, was most cost-effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:

    - UF and step-preferred ("in front of the step"): tolterodine ER (Detrol LA), oxybutynin IR (Ditropan, generics), and oxybutynin ER (Ditropan XL, generics). Prior authorization would require that all patients try Detrol LA, oxybutynin IR, or oxybutynin ER before TRICARE will cover the other agents in this drug class.
    - UF and non step-preferred ("behind the step"): trospium IR (Sanctura, generics), trospium ER (Sanctura XR, generics), tolterodine IR (Detrol, generics) and solifenacin (Vesicare)
        - When the generics to Sanctura, Sanctura XR, and Detrol become cost-effective relative to the step-preferred agents, the generics will become step-preferred without further action by the P&T Committee, Beneficiary Advisory Panel, or Director, TMA. A generic agent is cost-effective relative to step-preferred agents when the generic agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the step-preferred agent.
    - NF and non step-preferred: darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin TDS (Oxytrol), and oxybutynin 10% gel (Gelnique).

- Step therapy would apply to all users (current and new) of the OAB drugs.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining Detrol LA and oxybutynin ER on the BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) PA criteria for all current and new users of the OAB drugs, requiring a trial of Detrol LA, oxybutynin IR, or oxybutynin ER prior to the use of the other OAB drugs. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Enablex, Toviaz, Oxytrol, and Gelnique 10%. (See Appendix B for full MN criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is May 15, 2013.

   Addendum to the UF recommendation: During a post meeting bid review, it was determined that after-step bids should not be accepted and modeled due to verbiage in the bid solicitation. As a result of this determination, the cost analysis was recalculated. This new cost model was presented to the DoD P&T committee via electronic means. An electronic vote was taken to determine a) whether to accept the new cost review, maintain the current scenario and maintain current UF recommendations, or b) withdraw the UF recommendation, rebid the class and present results at the Feb 2013 meeting.

6. ***COMMITTEE ACTION: ADDENDUM TO UF RECOMMENDATION***
   The P&T Committee recommended (9 for, 5 opposed, 0 abstained, 3 absent) to approve the current scenario, which maintains the UF recommendation, step therapy requirements for all new and current users of OAB drugs, and PA criteria.

C. Gastrointestinal-2 Oral Antibiotic Drugs (GI-2)

Background and Relative Clinical Effectiveness—The Gastrointestinal-2 Oral Antibiotics (GI-2) Drug Class includes metronidazole (Flagyl, generics), vancomycin (Vancocin, generics), rifaximin (Xifaxan), fidaxomicin (Dificid), nitazoxanide (Alinia) and neomycin (Neo-Fradin, generics). This review focused on clinical effectiveness with regard to hepatic encephalopathy, *Clostridium difficile* infection, travelers' diarrhea, and non FDA-approved (off-label) uses. The class has not been previously reviewed for UF placement. The PORT provided the P&T Committee detailed analyses of current MHS prescription patterns. The data presented were factored into the relative clinical and cost-effectiveness determinations.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following concerning the GI-2 Drug Class:

- **Hepatic Encephalopathy (HE)**
  - Practice guidelines recommend lactulose as first line therapy for treatment of HE.
  - A Cochrane analysis found antibiotics, including rifaximin, were superior to lactulose in improving HE symptoms.
  - While rifaximin is approved for monotherapy, it is commonly used in combination with lactulose, and is better tolerated than lactulose.
- ***Clostridium difficile* Infection (CDI)**
  - Metronidazole is equally effective as vancomycin in treating mild to moderate CDI, but for severe CDI vancomycin results in higher clinical cure rates.
  - Fidaxomicin and vancomycin provide similar clinical cure rates for CDI; however, fidaxomicin decreases recurrence and increases global cure rates to a greater extent than vancomycin.
  - Comparative efficacy for nitazoxanide and rifaximin for CDI cannot be assessed, given the small numbers of trials.
- **Travelers' Diarrhea (TD)**
  - Practice guidelines recommend fluoroquinolones (e.g., levofloxacin, ciprofloxacin) as first line treatment for TD, unless contraindications exist.
  - A systematic review found ciprofloxacin more effective than rifaximin for prevention of TD.
  - Rifaximin's labeled indication is limited to treatment of TD caused by noninvasive strains of *Escherichia coli*. It is not effective for TD caused by Campylobacter, Shigella, and Salmonella species.
- **Off-label Uses**

- Rifaximin has been evaluated for irritable bowel syndrome (IBS) but is not approved by the FDA for IBS. In two studies, rifaximin showed modest (9%–12%) improvements in response rates compared to placebo; however, there was a significant placebo effect.
- Unanswered questions regarding use of rifaximin for IBS include the durability of response, efficacy for retreatment, prevention of recurrence, *C. difficile* emergence, bacterial resistance, and long-term side effects.
- Nonsupportable uses for rifaximin include CDI, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, rosacea, and any other non FDA-approved indication.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses, including CMA, were performed for the GI-2 Drug Class. Cost analyses were based on the disease states discussed in the clinical section. Comparative costs for agents from other drug classes were considered (e.g., lactulose, fluoroquinolones), due to the conclusions from the clinical effectiveness review. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following: for HE, lactulose was the least costly agent, followed by lactulose in combination with neomycin, and then rifaximin (Xifaxan). For CDI, metronidazole was the least costly agent, followed by vancomycin, with fidaxomicin (Dificid) as the most costly agent. For TD, ciprofloxacin was the least costly agent followed by rifaximin (Xifaxan) and nitazoxanide (Alinia).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (14 for, 2 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS.
    - UF: metronidazole, vancomycin, neomycin, rifaximin (Xifaxan), nitazoxanide (Alinia), and fidaxomicin (Dificid)
    - Fidaxomicin (Dificid) is available solely in the retail network. Availability of Dificid from mail order is not recommended due to the time constraints for treating acute *C. difficile* infection. Additionally, due to noncompliance with the Trade Agreements Act, Dificid is excluded from mail order and military treatment facilities (MTFs). Efforts to allow availability of Dificid at the MTFs is ongoing at this time.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) maintaining metronidazole 250 mg and 500 mg tablets on the BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) PA criteria for rifaximin (Xifaxan) 200 mg for TD. Automated PA criteria would require use of a fluoroquinolone prior to use of rifaximin 200 mg for travelers' diarrhea, unless the patient is under age 18, has a documented allergy to a fluoroquinolone, or is returning from an area with high fluoroquinolone resistance. The P&T Committee also recommended (14 for, 2 opposed, 1 abstained, 0 absent) PA criteria for rifaximin (Xifaxan) 550 mg for hepatic encephalopathy, consistent with the FDA-approved labeling. Other uses of rifaximin are not covered, including *C. difficile* infection, irritable bowel syndrome, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, and rosacea. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (15 for, 1 opposed, 1 abstained, 0 absent) QLs for the following GI-2 drugs:

    - Fidaxomicin (Dificid): 20 tablets with no refill in all POS, consistent with the product labeling
    - Rifaximin (Xifaxan) 200 mg: For travelers' diarrhea, if prior authorization is approved, a 3-day supply (9 tablets) in all three POS is recommended, consistent with the product labeling. For hepatic encephalopathy, if prior authorization is approved, overrides will be allowed.

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 90-day implementation period in all POS. Based in the P&T Committee's recommendation, the effective date is May 15, 2013.

D. Hepatitis C Drugs

Background and Relative Clinical Effectiveness—The Hepatitis C Drug Class includes the direct acting antiviral agents (DAAs) boceprevir (Victrelis) and telaprevir (Incivek); the interferon products PEG-interferon alfa-2a (Pegasys), PEG-interferon alfa-2b (PEG-Intron), and interferon alfacon-1(Infergen); and, various ribavirin products, including generics. Interferon alfa-2b (Intron A) is no longer used for treating hepatitis C virus infection and will not be discussed further. The PORT provided the P&T Committee detailed analyses of current MHS prescription patterns. The data presented were factored into the relative clinical and cost-effectiveness determinations.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following:

- Triple therapy with a direct acting antiviral agent (boceprevir or telaprevir), PEG-interferon, and ribavirin increases sustained viral response (SVR) rates to a greater extent than dual therapy with PEG-interferon and ribavirin (PR).
- There is insufficient evidence to conclude whether boceprevir (Victrelis) or telaprevir (Incivek) is superior to the other, due to the lack of direct comparative trials. Telaprevir offers patient convenience due to its shorter treatment course than boceprevir (12 weeks versus 44 weeks), but this has not resulted in higher SVR rates.
- There is insufficient evidence to support a preference of Pegasys over PEG-Intron, but there do not appear to be clinically relevant differences in efficacy.
- Interferon alfacon-1 (Infergen) has poor efficacy and is not included in current clinical practice guidelines. It no longer holds a niche in the treatment of prior null responders.
- Ribavirin is ineffective as monotherapy, but is critical to prevent relapse of hepatitis C virus infection.
- Compared with PR dual therapy, boceprevir triple therapy increases the risk for anemia and telaprevir triple therapy increases the risk for anemia and rash.
- Response-guided therapy for clinically appropriate patient populations maintains high levels of efficacy while shortening drug exposure times and treatment course duration.
- Overall drug discontinuations due to adverse events ranged from 8%–14% with telaprevir triple therapy versus 3% with PR dual therapy, and was 13% with boceprevir triple therapy versus 12% with PR dual therapy.
- With boceprevir, unique adverse events include dysgeusia, neutropenia, and psychiatric events, compared to anorectal adverse events (hemorrhoids, burning, itching) with telaprevir.

Relative Cost-Effectiveness Analysis and Conclusion—CMA was performed to compare each regimen for hepatitis C treatment (ribavirin, PEG-interferons, and DAAs). A cost-effectiveness analysis (CEA) was also performed comparing triple therapy (DAAs, PEG-interferon, and ribavirin) with dual therapy (PEG-interferon alfa and ribavirin). Additionally, a BIA was performed to compare competing formulary scenarios.

CMA results for the evaluated agents showed most dosage forms of ribavirin were generic and cost-effective. However, Ribapak was deemed not cost-effective compared with other ribavirin dosage forms. Both PEG-interferon alfa products (Pegasys and

PEG-Intron) had comparable costs. Interferon alfacon-1 (Infergen) was identified as not cost-effective when compared with the PEG-interferon agents. CMA results for the DAAs showed response-guided therapy could be less costly with boceprevir than with telaprevir, based on current dosing recommendations. However, when each agent was taken over its full treatment duration, telaprevir was less costly than boceprevir.

While insufficient evidence existed to establish a meaningful clinical difference in efficacy between the DAAs, the clinical effectiveness evaluation demonstrated that DAAs plus PEG-interferon alfa and ribavirin were more effective in combination than PEG-interferon alfa and ribavirin alone in inducing a SVR. The CEA concluded that combination use of DAAs plus PEG-interferon alfa and ribavirin was a cost-effective option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease who were previously untreated or for whom previous treatment had failed.

The BIA results suggested that designating ribavirin (Ribapak) and interferon alfacon-1 (Infergen) as NF on the UF was the most favorable scenario for the MHS.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that the most cost-effective scenario placed ribavirin (generics), PEG-interferon alfa-2a (Pegasys), interferon alfa-2b (Intron A), PEG-interferon alfa-2b (Peg-Intron), boceprevir (Victrelis), and telaprevir (Incivek) as formulary on the UF, and ribavirin (Ribapak) and interferon alfacon-1 (Infergen) as NF on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following:
    - UF status for boceprevir (Victrelis), telaprevir (Incivek), PEG-interferon alfa-2a (Pegasys), PEG-interferon alfa-2b (PEG Intron), interferon alfa-2b (Intron A), and ribavirin (except for the Ribapak formulation); and,
    - NF status for interferon alfacon-1 (Infergen) and the ribavirin Ribapak formulation, due to the lack of compelling clinical advantages and cost disadvantages when compared to the UF products.

2. ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) designating telaprevir (Incivek), PEG-interferon alfa-2a (Pegasys), and ribavirin 200 mg capsules (generics) as ECF products, based on clinical and cost-effectiveness.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for boceprevir (Victrelis) and telaprevir (Incivek), consistent with the FDA-approved labeling. Prior

authorization will expire after 12 weeks for telaprevir and 44 weeks for boceprevir. (See Appendix C for full criteria.)

4. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following QLs:

   - For boceprevir and telaprevir: a 28-day supply per prescription at all three POS, with no multiple fills for multiple co-pays; and,
   - For all the interferon and ribavirin products: a 90-day supply in MTFs and Mail Order, and a 30-day supply in the retail network.

5. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for interferon alfacon-1 (Infergen) and Ribapak. (See Appendix B for full MN criteria.)

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April, 17, 2013.

VI. RE-EVALUATION OF NF AGENTS

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to determine whether the UF status of agents designated as NF needs to be readdressed. The P&T Committee's process for the re-evaluation of NF agents established at the May 2007 meeting was approved by the Director, TMA on June 24, 2007, and is outlined in Appendix E.

The P&T Committee reevaluated the UF status of Lexapro (escitalopram) and pantoprazole (Protonix) in light of recent price reductions in the generic formulations across all three POS.

1. ***COMMITTEE ACTION: ESCITALOPRAM UF RECOMMENDATION AND IMPLEMENTATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) reclassification of escitalopram (Lexapro, generic) as formulary on the UF, as cost-effective generic formulations are now available in all three POS. Implementation will occur upon signing of the minutes.

2. ***COMMITTEE ACTION: PANTOPRAZOLE UF RECOMMENDATION AND IMPLEMENTATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) reclassification of pantoprazole (Protonix, generic) as formulary on the UF, as cost-effective generic formulations are now available in all three POS. Implementation will occur upon signing of the minutes.

VII. UTILIZATION MANAGEMENT

A. PAs

1. **Phosphodiesterase-5 (PDE-5) Inhibitors**—The PA criteria for the PDE-5 Inhibitor Drug Class was reviewed. Prior authorization allows use of a PDE-5 inhibitor following prostatectomy for preservation/restoration of erectile function for one year. There is no published evidence suggesting benefit if the PDE-5 inhibitor is initiated beyond one year after surgery. Recommendations were to clarify the existing PA criteria to state that prostatectomy surgery must have occurred less than 365 days from the date the PA form is signed.

   The additional recommendations were:

   - For Cialis: that existing criteria that apply to patients with benign prostatic hyperplasia (BPH) also apply to patients with BPH and erectile dysfunction (ED); and,
   - For sildenafil used for primary pulmonary hypertension (PPH): that the sildenafil dosage formulation specifically state 20 mg tablets to discourage use of sildenafil 20 mg tablets for ED.

   a) ***COMMITTEE ACTION: PDE-5 INHIBITOR PA CRITERIA***
   The P&T Committee recommended (14 for, 1 opposed, 2 abstained, 0 absent) PA criteria for the PDE-5 inhibitors (1) clarifying the existing PA criteria to state that prostatectomy surgery must have occurred less than 365 days from the date the PA form is signed; (2) for Cialis, that the existing criteria also apply to patients with BPH and ED; and, (3) for sildenafil for PPH, that the sildenafil dosage formulation will specifically state 20 mg tablets. (See Appendix C for full criteria.)

2. **Testosterone Replacement Therapy (TRT)**—PA criteria for the TRT Drug Class were developed at the August 2012 meeting and signed by the Director, TMA on November 8, 2012. The P&T Committee reviewed the PA criteria for use of TRT in women, which was based on level A evidence from the American College of Obstetrics and Gynecology, as outlined in a

2011 Clinical Bulletin. The Clinical Bulletin specifically mentions that there is little evidence to support long-term TRT use (longer than 6 months) in women.

a) ***COMMITTEE ACTION: TRT USE IN WOMEN PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the PA criteria for use of TRT in women to limit use to six months. (See Appendix C for full criteria.)

3. **Injectable Gonadotropins**—PA criteria currently apply to the injectable gonadotropins (fertility agents). Injectable gonadotropins are not covered under the TRICARE pharmacy benefit if they are being used in conjunction with a noncoital reproductive technology. In 2010, the Assistant Secretary of Defense for Health Affairs (ASD(HA)) authorized in vitro fertilization services for the benefit of severely or seriously ill/injured active duty service members. Implementation guidance for these services was developed in an April 2012 ASD(HA) policy.

   a) ***COMMITTEE ACTION: INJECTABLE GONADOTROPINS PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 2 abstained, 0 absent) revising the PA criteria for the injectable gonadotropins (fertility agents), to allow for use in conjunction with a noncoital reproductive technology, as outlined in the ASD(HA) April 2012 "Policy for Assisted Reproductive Services for the Benefit of Seriously or Severely Ill/Injured (Category II or III) Active Duty Service Members." A Signed Authorization Memorandum from TMA must be included with the prescription. (See Appendix C for full criteria.)

4. **Adalimumab (Humira)**—The FDA recently approved a new indication for Humira, the designated ECF agent in the targeted immunomodulatory biologics (TIBs) Drug Class. Humira is now indicated for the treatment of moderately to severely active ulcerative colitis following inadequate response to immunosuppressants such as corticosteroids, azathioprine, and 6-mercaptopurine.

   a) ***COMMITTEE ACTION: ADALIMUMAB (HUMIRA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) revising the existing PA criteria for Humira to

incorporate the new indication for ulcerative colitis, consistent with the FDA-approved product labeling. (See Appendix C for full criteria.)

5. **Enzalutamide (Xtandi) and Abiratone (Zytiga)**—Two new drugs for metastatic castration-resistant prostate cancer were recently approved. Xtandi and Zytiga are costly agents with specific FDA-indications, requiring use of prior docetaxel-containing regimens.

    a) ***COMMITTEE ACTION: ENZALUTAMIDE (XTANDI) AND ABIRATONE (ZYTIGA) PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) PA criteria for enzalutamide (Xtandi), and abiratone (Zytiga), consistent with the FDA-approved product labeling. (See Appendix C for full criteria.)

B. QLs

1. **Ipratropium/albuterol (Combivent Respimat)**—Ipratropium/albuterol (Combivent Respimat) oral inhaler is a non chlorofluorocarbon-containing reformulation of ipratropium and albuterol. The current chlorofluorocarbon (CFC) formulation, Combivent, will be phased out and replaced by Combivent Respimat. Combivent supplies are to be exhausted by December 31, 2013. The entire chronic obstructive pulmonary disease drug class will be reviewed formally for UF placement, including the BCF, at an upcoming meeting. Quantity limits currently apply to all oral inhalers.

    a) ***COMMITTEE ACTION: IPRATROPIUM/ALBUTEROL (COMBIVENT RESPIMAT) QL***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) QLs for Combivent Respimat, restricting the maximum allowable quantity at the retail point of service to 2 inhalers in 30 days and 5 inhalers in 90 days at Mail Order and MTFs, consistent with recommended dosing. (See Appendix D.)

2. **Azelastine/fluticasone propionate (Dymista), adalimumab (Humira), enzalutamide (Xtandi), and abiratone (Zytiga)**—The P&T Committee evaluated QLs for several other drugs, including azelastine/fluticasone propionate nasal inhaler (Dymista) (Nasal Allergy Drug Class), Humira for the new indication ulcerative colitis (TIBs Drug Class), and Xtandi and Zytiga (oral chemotherapy drugs for prostate cancer).

    a) ***COMMITTEE ACTION: DYMISTA, HUMIRA, XTANDI, AND ZYTIGA QL***—The P&T Committee recommended (16 for, 0 opposed, 1

abstained, 0 absent) QLs for Dymista, Humira for ulcerative colitis, Xtandi, and Zytiga, as outlined in Appendix D, consistent with FDA-approved product labeling.

VIII. SECTION 703

A. Section 703—The P&T Committee reviewed Kaon (branded potassium gluconate) and Pamine (branded methscopolamine) to determine MN and pre-authorization criteria. These two products were identified as not fulfilling refund requirements required in section 703 of the 2008 National Defense Authorization Act. These drugs were designated NF on the UF at previous P&T Committee meetings.

1. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following should apply to Kaon and Pamine. Coverage at retail network pharmacies would be approved if the patient met all of the following criteria:

   a) Manual Pre-Authorization Criteria:

      (1) Obtaining the product from home delivery would be detrimental to the patient.

      (2) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

   b) Implementation will occur upon signing of the minutes.

   The pre-authorization criteria listed above do not apply to any point of service other than retail network pharmacies.

VIII. OVERVIEWS

Two drug class overviews were presented to the P&T Committee, the oral anticoagulants (vitamin K antagonists, direct thrombin inhibitors, Factor Xa inhibitors), and the drugs for chronic obstructive pulmonary disease (COPD). Neither drug class has previously been reviewed for UF status. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

IX. ITEMS FOR INFORMATION

A. Joint Forces Pharmacy Seminar (JFPS) Presentation—The P&T Committee was briefed on spends and trends in MHS drug utilization, which was presented at the JFPS in October.

VIII. ADJOURNMENT

The meeting adjourned at 1130 hours on November 15, 2012. The next meeting will be in February 2013.

Appendix A—Attendance: November 2012 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria

Appendix C—Table of Prior Authorization Criteria

Appendix D—Table of Quantity Limits

Appendix E—Criteria for Re-evaluation of Nonformulary Drugs for Uniform Formulary Status

Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix G—Table of Abbreviations

Appendix A—Attendance: November 2012 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Octavio C. Mont, MS for COL John Spain, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CDR Aaron Middlekauf for CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
CAPT David Tanen, MC	Navy, Physician at Large
COL Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Jeremy King, MC	Air Force, OB/GYN Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
Maj Dan Castiglia, USAF	Defense Logistics Agency Troop Support

Appendix A—Attendance (continued)

Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
CDR Matthew Baker, USPHS	Indian Health Service
Adela Lucero	The MITRE Corporation
Isaac Armstrong	The MITRE Corporation
Lionel Levine	The MITRE Corporation
Others Present	
LTC Chris Conrad, MS	DoD Pharmacoeconomic Center
LCDR Marisol Martinez, USPHS	DoD Pharmacoeconomic Center
LCDR Joshua Devine, USPHS	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
Lt Col Melinda Henne, MC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Linh Quach, MSC	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe via DCO	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
LT Kendra Jenkins, USPHS	Pharmacy Resident
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Mr. Kirk Stocker	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Oxycodone IR (Oxecta) **High Potency Narcotic Analgesics**	• No formulary alternative: the patient requires a tamper resistant formulation of oxycodone IR
• Darifenacin (Enablex) • Fesoterodine (Toviaz) **Overactive Bladder (OAB) Drugs**	• Patient has experienced significant adverse effects from ALL of the formulary OAB medications (Detrol, oxybutynin IR/ER, Detrol IR, Sanctura IR/XR) that are not expected to occur with Enablex or Toviaz.
• Oxybutynin transdermal delivery system (Oxytrol) • Oxybutynin 10% gel (Gelnique) **Overactive Bladder (OAB) Drugs**	• Use of formulary agents is contraindicated. • Patient has experienced significant adverse effects from ALL of the formulary OAB medications that are not expected to occur with Oxytrol or Gelnique 10% (e.g., patient has experienced central nervous system adverse effects with the OAB drugs, but is expected to tolerate Oxytrol or Gelnique 10%). • There is no formulary alternative (e.g., patient requires an OAB drug and is unable to take oral medications).
• Interferon alfacon-1 (Infergen) **Hepatitis C Drugs**	• Use of ALL formulary PEG-interferon alfa-2 products is contraindicated (e.g., due to hypersensitivity), and treatment with Interferon alfacon-1 is not contraindicated. • The formulary agents have resulted in therapeutic failure.
• Ribavirin (Ribapak) **Hepatitis C Drugs**	• Use of ALL formulary ribavirin products is contraindicated (e.g., due to hypersensitivity), and treatment with Ribapak is not contraindicated.

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• exenatide twice daily (Byetta) • exenatide once weekly (Bydureon) • liraglutide once daily (Victoza) **Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)**	New GLP1RA users are required to try metformin or a sulfonylurea (SU) before receiving Byetta, Bydureon, or Victoza. Automated PA criteria: The patient has received a prescription for metformin or SU at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days, AND Manual PA criteria, if automated criteria are not met: Byetta, Bydureon, or Victoza is approved (e.g., trial of metformin or SU is NOT required) if: 1) The patient has a confirmed diagnosis of Type 2 Diabetes Mellitus 2) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis. 3) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment. 4) The patient has a contraindication to both metformin and a SU. 5) The patient has had an inadequate response to metformin and a SU.
• boceprevir (Victrelis) • telaprevir (Incivek) **Hepatitis C Drugs**	New users of boceprevir or telaprevir are required to undergo the PA process. Manual PA Criteria: • Age ≥ 18 • Has laboratory evidence of chronic hepatitis C—a quantified viral load (above undetectable) • Has laboratory evidence of genotype-1 hepatitis C infection • Is not co-infected with the human immunodeficiency virus (HIV) or Hepatitis B virus • Boceprevir or telaprevir will be co-administered with both a PEG-interferon alfa-2a or PEG-interferon alfa-2b product AND ribavirin • The patient has not previously used boceprevir or telaprevir. • For boceprevir, the patient will begin with a 4-week lead-in of both a PEG-Interferon alfa-2a or PEG-interferon alfa-2b product and ribavirin. Prior authorization will expire after 12 weeks for telaprevir and 44 weeks for boceprevir.

Appendix C—Table of PA Criteria (continued)

Drug / Drug Class	Prior Authorization Criteria
• tolterodine IR (Detrol, generics) • trospium IR (Sanctura, generics) • trospium ER (Sanctura XR, generics) • darifenacin (Enablex) • fesoterodine (Toviaz) • oxybutynin transdermal delivery system (Oxytrol) • oxybutynin 10% gel (Gelnique) • solifenacin (Vesicare) **Overactive Bladder (OAB) Drugs**	All new and current OAB drug users are required to try Detrol LA, oxybutynin ER, or oxybutynin IR before receiving Enablex, Toviaz, Detrol, Sanctura, Sanctura XR, Oxytrol, Gelnique 10%, or Vesicare. Automated PA criteria: The patient has received a prescription for Detrol LA, oxybutynin IR or oxybutynin ER at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days, AND Manual PA criteria, if automated criteria are not met (e.g., a trial of Detrol LA, oxybutynin IR, or oxybutynin ER is not required) if: 1) The patient has experienced any of the following issues while receiving Detrol LA, oxybutynin IR, or oxybutynin ER, which is not expected to occur with Detrol IR, Sanctura, Sanctura XR, Vesicare, Enablex, Toviaz, Oxytrol, or Gelnique 10%: – inadequate response; – intolerable adverse effects (e.g., the patient requires Sanctura due to intolerable dry mouth with Detrol LA); or, – contraindication. Coverage is only approved for the following FDA-approved indications: 1) The patient has a confirmed diagnosis of OAB with symptoms of urge incontinence, urgency, and urinary frequency (for all 11 OAB drugs). 2) The patient is older than 6 years with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida), for oxybutynin ER. Other uses, including stress incontinence, will not be approved.

Appendix C—Table of PA Criteria (continued)

Drug / Drug Class	Prior Authorization Criteria
• Rifaximin (Xifaxan) 200 mg **Gastrointestinal-2 Oral Antibiotics (GI-2)**	New users of Xifaxan 200 mg for travelers' diarrhea are required to undergo the PA process. Automated PA Criteria: The patient has received a prescription for a fluoroquinolone at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 60 days, AND Manual PA Criteria: • 200 mg tablets are approved for the following: – Documented use in travelers' diarrhea caused by noninvasive strains of *Escherichia coli* – Patient is between 12 and 18 years of age – Documented trial of a fluoroquinolone for patients > 18 years of age – Documented contraindication or allergy to fluoroquinolone antibiotics in last 60 days – Returning from area with high fluoroquinolone resistance – 200 mg tablets are being used to treat hepatic encephalopathy • 200 mg tablets are not approved for the following: – Diarrhea complicated by fever or bloody stool – Treatment of dysentery – Diarrhea associated with use of antibiotics – Diarrhea caused by bacteria other than *E. coli* – *C. difficile* infection, irritable bowel syndrome, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, rosacea, and any other non-FDA approved use If prior authorization is approved for travelers' diarrhea, the quantity is limited to a 3-day supply (200mg TID = 9 tablets) at all 3 points of service.
• Rifaximin (Xifaxan) 550 mg **Gastrointestinal-2 Oral Antibiotics (GI-2)**	New users of Xifaxan 550 mg for hepatic encephalopathy are required to undergo the PA process. Manual PA Criteria: • 550 mg tablets are approved for the following: – Documented use in hepatic encephalopathy • 550 mg tablets are not approved for the following: – Travelers' diarrhea, *C. difficile* infection, irritable bowel syndrome, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, rosacea, and any other non-FDA approved use Prior authorization will expire after 365 days.

Appendix C—Table of PA Criteria (continued)

Drug / Drug Class	Prior Authorization Criteria
• sildenaril (Viagra) • tadalafil (Cialis) • vardenaril (Levitra; Staxyn) **Phosphodiesterase-5 (PDE-5) Inhibitors**	**Post-Prostatectomy:** Coverage IS provided for: • Sildenafil (Viagra), vardenafil (Levitra), or tadalafil (Cialis) for preservation and/or restoration of erectile function post-prostatectomy **Prostatectomy surgery must have occurred less than 365 days from the date the PA form is signed.** ***(recommended at Nov 2012 meeting)*** **BPH or BPH with ED:** Coverage IS provided for: • Tadalafil 5 mg (Cialis 5mg) for patients with benign prostatic hyperplasia (BPH) or **BPH with erectile dysfunction (ED)** meeting prior authorization criteria requiring use of an alpha blocker, unless there is a contraindication, inadequate response, or intolerable adverse effects with the alpha blocker. ***(recommended at Nov 2012 meeting)*** **Primary Pulmonary Hypertension:** Coverage IS provided for: • Sildenafil **20 mg** (Revatio) or tadalafil (Adcirca) for any patient with primary pulmonary hypertension ***(recommended at Nov 2012 meeting)***
• transdermal 2% gel pump (Fortesta) • transdermal solution (Axiron) • transdermal patch (Androderm) • transdermal 1.62% gel pump (Androgel 1.62%) • transdermal 1% gel pump and gel packets (Androgel 1%) • transdermal gel tubes (Testim) • testosterone buccal tablets (Striant) **Testosterone Replacement Therapy (TRT)**	PA criteria required for all topical/buccal TRT products • Men: diagnosis of hypogonadism evidenced by 2 or more AM testosterone levels in presence of symptoms • Children – under age of 17 – not approved – appeal only • Women: – Treatment of hypoactive sexual desire in menopausal women (natural or surgical) – Treatment of menopausal symptoms in women also receiving FDA-approved estrogen products (with or without concomitant progesterone) – **Treatment limited to 6 months** ***(recommended at Nov 2012 meeting)*** – TRT not approved for osteoporosis or urinary incontinence – Coverage for women upon appeal
• Enzalutamide (Xtandi) **Oral Chemotherapy Drugs for Prostate Cancer**	Coverage approved for treatment of patients: ▪ With a documented diagnosis of metastatic castration-resistant prostate cancer, AND ▪ Previous treatment with docetaxel
• Abiratone (Zytiga) **Oral Chemotherapy Drugs for Prostate Cancer**	Coverage approved for treatment of patients: ▪ With a documented diagnosis of metastatic castration-resistant prostate cancer, AND ▪ Prior chemotherapy with docetaxel, AND ▪ Patient is receiving concomitant therapy with prednisone

Appendix C—Table of PA Criteria (continued)

Drug / Drug Class	Prior Authorization Criteria
• follitropin alfa (Gonal-F) • follitropin beta (Follistim, Follistim AQ) • menotropins (Humegon, Pergonal, Repronex) • urofollitropin (Fertinex, Bravelle) **Injectable Gonadotropins (Fertility Agents)**	These drugs are not covered under the TRICARE pharmacy benefit if they are being prescribed for use in conjunction with a noncoital reproductive technology, including but not limited to artificial insemination, in vitro fertilization, or gamete intrafallopian transfer The TRICARE family planning benefit outlined in the Code of Federal Regulations does not include services and supplies related to noncoital reproductive technologies. • **Coverage for fertility drugs is allowed for use in conjunction with a noncoital reproductive technology, as outlined in the April 2012 ASD (Health Affairs) "Policy for Assisted Reproductive Services for the Benefit of Seriously or Severally Ill/Injured (Category II or III) Active Duty Service Members." A Signed Authorization Memorandum from TMA must be included with the prescription *(recommended at Nov 2012 meeting).***
• Adalimumab (Humira) **Targeted Immunomodulatory Biologics (TIBs)**	Coverage approved for patients ≥ 18 years with: ▪ Moderate to severely active rheumatoid arthritis and psoriasis, active psoriatic arthritis, and active ankylosing spondylitis ▪ Moderate to severely active polyarticular juvenile idiopathic arthritis (pediatric patients: 4 to 17 years of age) ▪ Moderate to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to infliximab or an inability to tolerate infliximab ▪ **Moderately to severely active ulcerative colitis following inadequate response to immunosuppressants (e.g., corticosteroids, azathioprine and 6-mercaptopurine) *(recommended at Nov 2012 meeting)*** Coverage NOT approved for: ▪ Concomitant use with other TIBs (anakinra, abatacept, certolizumab pegol, etanercept, infliximab, and golimumab)

Appendix D—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
• fidaxomicin (Dificid) **Gastrointestinal-2 Oral Antibiotics (GI-2)**	• Retail, Mail Order, and MTF: 20 tablets with no refills
• rifaximin (Xifaxan) 200 mg tablets **Gastrointestinal-2 Oral Antibiotics (GI-2)**	If Prior Authorization is approved: • Retail, Mail Order and MTF: 3-day supply (9 tablets) for travelers' diarrhea; overrides allowed for hepatic encephalopathy
• boceprevir (Victrelis) • telaprevir (Incivek) **Hepatitis C Agents**	• Retail, Mail Order, and MTF: 28-day supply, with no multiple fills for multiple co-pays
• ribavirin (all products, including generics, Copegus, Rebetol, Ribasphere, Ribapak) • Interferon alfa-2b (Intron A) • Interferon alfacon-1 (Infergen) • PEG-interferon alfa-2a (Pegasys) • PEG-interferon alfa-2b (PEG-Intron) **Hepatitis C Agents**	• Retail Network: 30-day supply • Mail Order and MTF: 90-day supply
• ipratropium/albuterol oral inhaler (Combivent Respimat) **Chronic Obstructive Pulmonary Disease (COPD) Drugs**	• Retail: 2 inhalers/30 days • Mail Order and MTF: 5 inhalers/90 days
• azelastine/fluticasone propionate nasal inhaler (Dymista) **Nasal Allergy Drugs**	• Retail: 1 inhalers/30 days • Mail Order and MTF: 3 inhalers/90 days
• adalimumab (Humira) **Targeted Immunomodulatory Biologics (TIBs)**	Ulcerative Colitis • Initiation of therapy: o Retail, Mail Order, and MTF: 6 syringes • Maximum quantity dispensed at any one time: o Retail: 4-week supply (2 packs of 2 syringes) o Mail order and MTF: 6-week supply (3 packs of 2 syringes)
• enzalutamide (Xtandi) **Oral Chemotherapy Drugs for Prostate Cancer**	• Retail: 30-day supply (120 capsules) • Mail Order and MTF: 45-day supply (180 capsules)
• abiratone (Zytiga) **Oral Chemotherapy Drugs for Prostate Cancer**	• Retail: 30-day supply (120 tablets) • Mail Order and MTF: 45-day supply (180 tablets)

Appendix E—Criteria for Re-evaluation of Nonformulary Drugs for Uniform Formulary Status

The P&T Committee's process for the re-evaluation of nonformulary (NF) agents established at the May 2007 meeting was approved by the Director, TMA on June 24, 2007, according to the criteria below:

1) The NF agent becomes generically available and
   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system.
   b) The generic market supply is stable and sufficient to meet the DoD Military Health System supply demands.
2) The NF agent is cost-effective relative to similar agents on the Uniform Formulary (UF). A NF agent becomes cost-effective when:
   a) The NF agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
   b) The NF agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2012	**Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)**	UF Class Review	None	▪ exenatide BID injection (Byetta) ▪ exenatide once weekly injection (Bydureon) ▪ liraglutide once daily injection (Victoza)	N/A	Pending signing of the minutes/ 30 days	PA apply	▪ Current requirement for trial of metformin or a sulfonylurea prior to a GLP1RA still applies. ▪ Byetta is no longer the preferred GLP1RA (the previous step therapy requiring use of Byetta prior to another GLP1RA has been removed).
Nov 2012	**Overactive Bladder Drugs (OABs)**	UF Class Review	▪ Tolterodine ER (Detrol LA)* ▪ Oxybutynin ER (Ditropan XL, generics)* *step-preferred	▪ oxybutynin IR (Ditropan, generics)* ▪ solifenacin (Vesicare) ▪ trospium IR (Sanctura, generics) ▪ trospium ER (Sanctura ER, generics) ▪ tolterodine IR (Detrol IR, generics) *step-preferred	▪ fesoterodine (Toviaz) ▪ darifenacin (Enablex) ▪ oxybutynin transdermal delivery system (Oxytrol) ▪ oxybutynin 10% gel (Gelnique)	Pending signing of the minutes/ 90 days	Step therapy (Automated PA); requires trial of Detrol LA, oxybutynin IR, or oxybutynin ER (step-preferred drugs) prior to another OAB drug.	▪ When generic formulations of trospium IR (Sanctura), trospium ER (Sanctura ER), and tolterodine IR (Detrol) become cost-effective relative to the step-preferred drugs, they will become step-preferred.

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2012	**Gastrointestinal-2 Oral Antibiotics (GI-2s)**	UF Class Review	▪ metronidazole 250 mg & 500 mg tabs (Flagyl, generics)	▪ fidaxomicin (Dificid)* ▪ metronidazole 375 mg, 750 mg ER tabs (Flagyl, Flagyl ER, generics) ▪ neomycin (Neo-Fradin, generics) ▪ nitazoxanide (Alinia) ▪ rifaximin (Xifaxan) ▪ vancomycin 125 mg, 250 mg oral tabs (Vancocin, generics) *Dificid not available at Mail or MTFs	N/A	Pending signing of the minutes/ 90 days	▪ PA recommendation for rifaximin, limiting use to hepatic encephalopathy (365 days) & traveler's diarrhea (3 days) (See Appendix C) ▪ QLs recommendation for fidaxomicin and rifaximin	▪ QLs for fidaxomicin #20 tabs with no refill ▪ QLs for rifaximin 200 mg #9 tabs with no refills ▪ fidaxomicin (Dificid) not available at Mail Order or MTFs
Nov 2012	**Hepatitis C Drugs**	UF Class Review	Extended Core Formulary (ECF)*: ▪ telaprevir (Incivek) ▪ PEG-interferon alfa-2a (Pegasys) ▪ ribavirin 200 mg capsules (generics); excludes Ribapak formulation	▪ boceprevir (Victrelis) ▪ interferon alfa-2b (Intron A) ▪ PEG-interferon alfa-2b (PEG-Intron) ▪ ribavirin (Copegus, Rebetol, Ribasphere)	▪ interferon alfacon-1 (Infergen) ▪ ribavirin Ribapak formulation	Pending signing of the minutes/60 days	▪ PA recommendation for boceprevir and telaprevir (See Appendix C) ▪ QL recommendation for boceprevir, telaprevir, interferon products, and ribavirin	▪ QLs for boceprevir & telaprevir: 28-day supply at all 3 POS; no multiple fills for multiple co-pays ▪ QL recommendation for interferon products and ribavirin: 90-day supply in MTFs and Mail Order; 30-day supply at retail

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2012	**Narcotic Analgesics** **Subclass: High potency Single Analgesic Agents**	New Drugs in Already Reviewed Class	High potency single analgesic agents ▪ Morphine sulfate 12 hours ER (MS Contin, generics) ▪ Morphine sulfate IR	Previous Decisions ▪ Hydromorphone ER (Exalgo) ▪ Fentanyl buccal soluble film (Onsolis) ▪ Fentanyl transdermal system, transmucosal tablet (Fentora); and, transmucosal lozenge ▪ Hydromorphone (Dilaudid) ▪ Levorphanol ▪ Meperidine ▪ Methadone ▪ Morphine products (other than BCF), Kadian and Avinza (ER products) ▪ Morphine sulfate ER / naltrexone (Embeda) ▪ Opium tincture ▪ Opium/belladonna alkaloids(suppositories) ▪ Oxycodone IR ▪ Oxycodone ER (Oxycontin) ▪ Oxymorphone (Opana) ▪ Oxymorphone ER (Opana ER) ▪ Tapentadol extended release (Nucynta ER) (Feb 2012)	**oxycodone IR (Oxecta)** Tapentadol immediate release (Nucynta) (Nov 2009)	Pending signing of the minutes/ 60 days	-	-

* **Extended Core Formulary (ECF):** includes medications in therapeutic classes that are used to support more specialized scopes of practice than those on the BCF. MTFs may choose whether or not to include an ECF therapeutic class on formulary, based on the clinical needs of its patients. However, if an MTF chooses to have an ECF therapeutic class on formulary, it must have all ECF medications in that class on formulary.

TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix G—Table of Abbreviations

ASD(HA)	Assistant Secretary of Defense for Health Affairs
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPH	benign prostatic hyperplasia
CEA	cost-effectiveness analysis
CFC	chlorofluorocarbon
CDI	*Clostridium difficile* infection
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DAAs	direct acting antiviral agent
DoD	Department of Defense
E. coli	*Escherichia coli*
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
FDA	U.S. Food and Drug Administration
GI-2	Gastrointestinal-2 Oral Antibiotics Drug Class
GLP1RAs	glucagon-like peptide-1 receptor agonists
HE	hepatic encephalopathy
IBS	irritable bowel syndrome
IR	immediate release
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
OAB	Overactive Bladder Drug Class
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE-5	phosphodiesterase-5
PEC	Pharmacoeconomic Center
PORT	Pharmacy Outcomes Research Team
POS	points of service
PPH	primary pulmonary hypertension
PR	PEG-interferon with ribavirin
QLs	quantity limits
SVR	sustained viral response
TIBs	targeted immunomodulatory biologics
TD	travelers' diarrhea
TDS	transdermal delivery system
TRTs	transdermal and buccal testosterone replacement therapies
UF	Uniform Formulary

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2012

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Targeted Immunomodulatory Biologics (TIBs)—Abatacept Subcutaneous (SC) Injection (Orencia SC)

Relative Clinical Effectiveness Conclusion—The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that although abatacept SC (Orencia SC) provides an alternative to the tumor necrosis factor (TNF) alpha inhibitors used for treatment of rheumatoid arthritis and offers patient convenience over the abatacept intravenous formulation, there is currently insufficient data to conclude that Orencia SC offers improved efficacy, safety, or tolerability compared to the TNF alpha inhibitors in the TIBs class.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that abatacept SC (Orencia SC) was not cost-effective when compared to other TIBs included on the Uniform Formulary (UF).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) abatacept SC (Orencia SC) be designated nonformulary (NF) due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***
Based on the clinical evaluations for abatacept SC (Orencia SC) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for abatacept SC (Orencia SC). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Glaucoma Drugs: Prostaglandin Analogs—Tafluprost Ophthalmic Solution (Zioptan)

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) that tafluprost (Zioptan) offers no compelling clinical advantages over the other prostaglandins available on the UF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that tafluprost (Zioptan) was not cost-effective when compared to the other ophthalmic prostaglandins currently included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) tafluprost (Zioptan) be designated NF because it has no compelling clinical advantages over the other ophthalmic prostaglandin analogues and is not cost-effective compared to latanoprost, the most utilized drug in the Military Health System (MHS).

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for tafluprost (Zioptan) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for tafluprost (Zioptan). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Oral Non-steroidal Anti-inflammatory Drugs (NSAIDs)—Ibuprofen/Famotidine (Duexis)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) ibuprofen/famotidine (Duexis) offers no distinct clinical advantages to the combination NSAID/gastroprotective agents already on the UF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that ibuprofen/famotidine (Duexis) was not cost-effective when compared to other oral NSAIDs agents included on the UF; it was also more costly than the individual components, ibuprofen and famotidine.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) ibuprofen/famotidine (Duexis) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for ibuprofen/famotidine (Duexis) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for ibuprofen/famotidine (Duexis). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013

Director, TMA, Decision: ☒Approved ☐ Disapproved

Approved, but modified as follows:

D. Oral NSAIDs—Ketorolac Nasal Spray (Sprix)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) there is no evidence to suggest ketorolac nasal spray

(Sprix) has a compelling clinical advantage over the other oral NSAIDs already on the Basic Core Formulary (BCF) and UF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that ketorolac nasal spray (Sprix) was more costly, based on an average weighted cost per day of therapy at all three points of service (POS), than the other oral NSAIDs and low-potency narcotic analgesics currently on the BCF and UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (16 for, 0 opposed, 1 abstained, 0 absent) ketorolac nasal spray (Sprix) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for ketorolac nasal spray (Sprix) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for ketorolac nasal spray (Sprix). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: QUANTITY LIMITS***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 0 absent) restricting the maximum allowable quantity to 5 nasal spray bottles/30 days in the mail order pharmacy and retail network, which is consistent with the recommended dosing from the package labeling.

4. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

E. Non-Insulin Diabetes Drugs: Dipeptidyl Dipeptidase-4 (DPP-4) Inhibitors—Sitagliptin/Metformin ER (Janumet XR) and Linagliptin/ Metformin (Jentadueto)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) there is no evidence to suggest either sitagliptin/ metformin ER (Janumet XR) or linagliptin/metformin (Jentadueto) have a compelling clinical advantage over the other DPP-4 inhibitor/metformin fixed-dose combinations included on the UF.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that Janumet XR and Jentadueto were cost-effective when compared to other DPP-4 inhibitors included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (15 for, 0 opposed, 1 abstained, 1 absent) the following:

    - sitagliptin/metformin ER (Janumet XR) be designated step-preferred and formulary on the UF; and
    - linagliptin/metformin (Jentadueto) be designated non-preferred and formulary on the UF.
    - This recommendation includes step therapy, which requires a trial of sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/ simvastatin (Juvisync), or sitagliptin/metformin ER (Janumet XR) (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors also requires a trial of metformin or sulfonylurea for new patients.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee, recommended (14 for, 1 opposed, 1 abstained, 1 absent) sitagliptin/metformin ER (Janumet XR) be designated with BCF status.

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria

    a) Automated PA criteria:

        (1) The patient has filled a prescription for metformin or a sulfonylurea at any MHS pharmacy POS [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

(2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Janumet XR, Tradjenta, Jentadueto, Onglyza, or Kombiglyze XR) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria, if automated criteria are not met:

The fixed-dose combination product Janumet XR or Jentadueto is approved (eg, a trial of sulfonylurea is not required if):

(1) The patient has had an inadequate response to metformin or sulfonylurea.

(2) The patient has experienced the following adverse event while receiving a sulfonylurea: hypoglycemia requiring medical treatment.

(3) The patient has a contraindication to a sulfonylurea.

c) In addition to the above criteria regarding metformin and sulfonylurea, the following PA criteria would apply specifically to linagliptin/metformin metformin (Jentadueto):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENATION PERIOD***
The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

II. UNIFORM FORMULARY DRUG CLASS REVIEWS

A. Anticoagulants—Heparin and Related Products

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 2 absent) on the following clinical effectiveness conclusions:

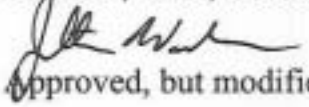
- Enoxaparin (Lovenox, generic) has the widest clinical utility of the subclass, due to its long history of use and largest number of FDA-approved indications.
- Fondaparinux (Arixtra, generic) has fewer FDA-approved indications than enoxaparin. It has a therapeutic niche for patients with a history of heparin-induced thrombocytopenia (HIT).
- The major limitation with dalteparin (Fragmin) is the lack of an FDA-approved indication for treating deep venous thrombosis and pulmonary embolism. The package insert also cautions against use in patients with a history of HIT.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that generic enoxaparin was the most cost-effective agent based on a weighted average cost per unit across all three POS, followed by branded dalteparin (Fragmin), and generic fondaparinux. Budget impact analysis (BIA) results showed that scenarios where generic enoxaparin is included on the BCF and dalteparin (Fragmin) and generic fondaparinux are included on the UF generated the greatest cost-avoidance projection.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (15 for, 0 opposed, 1 abstained, 1 absent) enoxaparin, dalteparin (Fragmin), and fondaparinux remain designated as formulary on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) generic enoxaparin be designated with BCF status, based on clinical and cost effectivness. The BCF recommendation will be implemented upon signing of the minutes.

Director, TMA, Decision: ☒ Approved ☐ Disapproved



Approved, but modified as follows:

B. Androgens Anabolic Steroids—Transdermal and Buccal Testosterone Replacement Therapies (TRTs)

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the following concerning the TRT agents:

- Although high-quality comparative data is lacking, there appear to be no clinically relevant differences in efficacy between products.
- Transdermal and buccal testosterone replacement products effectively raise testosterone levels in hypogonadal men to the normal range when used in accordance with product labeling.
- Skin-to-skin transfer of transdermal testosterone to women and children should be minimized due to risk of virilization or premature onset of puberty. Testosterone buccal tablets (Striant) carry the lowest risk while the topically applied products carry the highest risk.
- Transdermal and buccal TRTs have a low overall incidence of systemic adverse events, which are not considered to differ clinically across products.
- The most frequent adverse events are dermal application site reactions for the transdermal products and oral application site reactions for buccal tablets; most are mild or transient in nature.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that transdermal 2% gel pump (Fortesta) was the least costly agent, followed by transdermal solution (Axiron), transdermal patch (Androderm), transdermal 1.62% gel pump (Androgel 1.62%), transdermal 1% gel pump and gel packets (Androgel 1%), transdermal gel tubes (Testim), and testosterone buccal tablets (Striant).

BIA results showed the scenario where transdermal 2% gel (Fortesta) is step-preferred on the UF, all other TRTs are designated non-preferred on the UF or NF, and step therapy is applied to all current and new users of TRTs, was determined to be the most cost-effective scenario.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (13 for, 3 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS:
    - testosterone transdermal 2% gel pump (Fortesta) be designated step-preferred and formulary on the UF;
    - testosterone transdermal patch (Androderm), testosterone transdermal gel tubes (Testim), and testosterone buccal tablets (Striant) be designated non-preferred and formulary on the UF; and
    - testosterone transdermal 1% gel pump and gel packets (Androgel 1%), testosterone transdermal 1.62% gel pump (Androgel 1.62%), and

testosterone transdermal solution (Axiron) be designated non-preferred and NF on the UF.

- This recommendation includes step therapy, which requires a trial of testosterone transdermal 2% gel pump (Fortesta) prior to using other transdermal and buccal TRTs.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) testosterone transdermal 2% gel pump (Fortesta) be designated BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 4 absent) that the following manual PA criteria should apply to all current and new users of the testosterone replacement therapies. Coverage would be approved if the patient met any of the following criteria:

   a) Manual PA criteria for all transdermal and buccal testosterone replacement products:

      - Patient is male and has a diagnosis of hypogonadism evidenced by 2 or more morning testosterone levels in the presence of symptoms usually associated with hypogonadism.
      - Patient is a female and receiving testosterone for the following uses:
        - Treatment of hypoactive sexual desire in menopausal women (whether natural or surgical); or
        - Treatment of menopausal symptoms in women also receiving FDA-approved estrogen products (with or without concomitant progesterone).
        - Note that coverage of transdermal or buccal testosterone replacement therapies is not approved for osteoporosis or urinary incontinence.
        - Note that coverage for use in women will be by appeal only.
      - Note that use in adolescents under the age of 17 is not approved and will be by appeal only.

   b) In addition to the above criteria, the following PA criteria would apply specifically to transdermal gel tubes (Testim), transdermal patch (Androderm), buccal tablets (Striant), transdermal 1% gel pump and gel

packets (Androgel 1%), transdermal 1.62% gel pump (Androgel 1.62%), and transdermal solution (Axiron):

- The patient requires a testosterone replacement therapy that has a low risk of skin-to-skin transfer between family members (for Striant and Androderm only).
- The patient has tried transdermal 2% gel pump (Fortesta) for a minimum of 90 days AND failed to achieve total testosterone levels above 400ng/dL (lab must be drawn 2 hours after Fortesta application) AND denied improvement in symptoms.
- The patient has a contraindication or relative contraindication to Fortesta (e.g., hypersensitivity to a component [including alcohol]; concomitant disulfiram use) that does not apply to Testim, Androderm, Striant, Androgel 1%, Androgel 1.62%, or Axiron.
- The patient has experienced a clinically significant skin reaction to Fortesta that is not expected to occur with Testim, Androderm, Striant, Androgel 1%, Androgel 1.62%, or Axiron.

4. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for transdermal 1.62% gel pump (Androgel 1.62%), transdermal 1% gel pump and gel packets (Androgel 1%), the transdermal solution (Axiron), and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Androgel 1.62%, Androgel 1%, and Axiron. (See Appendix B for full MN criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is February 6, 2013.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

III. SECTION 703

A. Section 703—The P&T Committee reviewed a list of products—Amicar (branded aminocaproic acid), Kineret (anakinra), Phoslo (branded calcium acetate), Rheumatrex (branded methotrexate), Oxadrin (branded oxandrolone), Denavir (penciclovir), and Transderm-Scop (scopolamine patch)—to determine MN and pre-authorization criteria. These products were identified as not fulfilling refund requirements as required in section 703 of the 2008 National Defense Authorization Act. These drugs were made NF on the UF at previous P&T Committee meetings.

1. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 4 absent) the following should apply to the drugs listed above. Coverage at retail network pharmacies would be approved if the patient met all the following criteria:

    a) Manual Pre-Authorization Criteria:

    (1) Obtaining the product from home delivery would be detrimental to the patient.

    (2) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

The Pre-Authorization criteria listed above do not apply to any point of service other than retail network pharmacies.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

NOV 8 2012

Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

August 2012

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 15 and 16, 2012, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May Minutes**—Jonathon Woodson M.D., Director, approved the minutes for the May 2012 DoD P&T Committee meeting on August 8, 2012.
2. **Clarification to the February 2012 Minutes**—The February minutes were clarified to state, for the Sedative Hypnotics-1 class, zolpidem IR is the sole Basic Core Formulary (BCF) drug.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and BCF recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Targeted Immunomodulatory Biologics (TIBs)—Abatacept Subcutaneous Injection (Orencia SC)

Relative Clinical Effectiveness—Abatacept (Orencia) inhibits the activation of T-cells and is approved for treating moderate to severe active rheumatoid arthritis (RA) in adults. It was first marketed in 2005 as an intravenous (IV) infusion, which is only available through the TRICARE medical benefit. A new subcutaneous (SC) abatacept

formulation intended for self-injection is now available. FDA-approval of abatacept SC was based on its demonstrated non-inferiority to abatacept IV. Prior authorization criteria and quantity limits apply to the TIBs and were placed on abatacept SC in November 2011, which are consistent with the FDA-approved package labeling.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that although abatacept SC (Orencia SC) provides an alternative to the tumor necrosis factor (TNF) alpha inhibitors used for treatment of RA and offers patient convenience over the abatacept IV formulation, there is currently insufficient data to conclude that Orencia SC offers improved efficacy, safety, or tolerability compared to the TNF alpha inhibitors in the TIBs class.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per month at all three points of service (POS) was evaluated for abatacept SC (Orencia SC) in relation to the other drugs in the TIBs class indicated for treatment of RA. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Orencia SC was not cost-effective when compared to other TIBs included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) abatacept SC (Orencia SC) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for abatacept SC (Orencia SC) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for abatacept SC (Orencia SC). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

B. Glaucoma Drugs: Prostaglandin Analogs—Tafluprost Ophthalmic Solution (Zioptan)

Relative Clinical Effectiveness—Tafluprost ophthalmic solution (Zioptan) is a preservative-free prostaglandin analog indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension. In one head-to-head comparison, tafluprost proved inferior to latanoprost in lowering IOP, failing to meet the pre-specified margin for non-inferiority. Whether preservative-free tafluprost is associated with decreased adverse events compared to preservative-containing tafluprost remains to be determined.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) that tafluprost (Zioptan) offers no compelling clinical advantages over the other prostaglandins available on the UF.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per day at all three POS was evaluated for tafluprost (Zioptan) in relation to the other ophthalmic prostaglandin analogues. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Zioptan was not cost-effective when compared to the other ophthalmic prostaglandins currently included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) tafluprost (Zioptan) be designated NF because it has no compelling clinical advantages over the other ophthalmic prostaglandin analogues and is not cost-effective compared to latanoprost, the most utilized drug in the Military Health System (MHS).

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for tafluprost (Zioptan) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for tafluprost (Zioptan). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9,

2013.

C. Oral Non-steroidal Anti-inflammatory Drugs (NSAIDs)—Ibuprofen/Famotidine (Duexis)

Relative Clinical Effectiveness—Ibuprofen/famotidine (Duexis) is the first fixed-dose combination of a non-selective NSAID with an H2 antagonist. Ibuprofen and famotidine are currently on the BCF and UF, respectively, and are available over-the-counter. Other combination NSAID/gastroprotective agents on the UF include esomeprazole/enteric-coated naproxen (Vimovo), diclofenac/misoprostol (Arthrotec), and the COX-2 inhibitor celecoxib (Celebrex). No studies with Duexis have evaluated clinically important upper GI events (bleeding, perforation, obstruction). Although the fixed-dose combination of famotidine and ibuprofen offers the convenience of a gastroprotective agent with an NSAID, the three-times daily dosing regimen may affect patient compliance. Systematic reviews and national professional guidelines state a preference for NSAID with proton pump inhibitor or NSAID with misoprostol versus an NSAID with H2 antagonist for reducing GI ulcers.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) ibuprofen/famotidine (Duexis) offers no distinct clinical advantages to the combination NSAID/gastroprotective agents already on the UF.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per day at all three POS was evaluated for ibuprofen/famotidine (Duexis) in relation to the other oral gastroprotective NSAIDs. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that Duexis was not cost-effective when compared to other oral NSAIDs agents included on the UF; it was also more costly than the individual components, ibuprofen and famotidine.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) ibuprofen/famotidine (Duexis) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for ibuprofen/famotidine (Duexis) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for ibuprofen/famotidine (Duexis). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

D. Oral NSAIDs—Ketorolac Nasal Spray (Sprix)

Relative Clinical Effectiveness—Ketorolac nasal spray (Sprix) is the first NSAID administered by the intranasal route. There is no direct comparative data with ketorolac nasal spray or other oral NSAIDs or low potency narcotic analgesics. The studies used to obtain FDA-approval were conducted using a placebo control in the in-patient setting where concomitant morphine or rescue analgesia was administered. Reduced morphine requirements were seen at 24 hours in some studies with Sprix—whether these results are clinically relevant is difficult to determine. Opioid-sparing drugs on the UF include other NSAIDs and tramadol. Sprix is limited by a five-day duration of use, and warnings not seen with other NSAIDs, including contraindications for use in patients with a history of GI bleeding or renal dysfunction.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) there is no evidence to suggest ketorolac nasal spray (Sprix) has a compelling clinical advantage over the other oral NSAIDs already on the BCF and UF.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that ketorolac nasal spray (Sprix) was more costly, based on an average weighted cost per day of therapy at all three POS, than the other oral NSAIDs and low-potency narcotic analgesics currently on the BCF and UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (16 for, 0 opposed, 1 abstained, 0 absent) ketorolac nasal spray (Sprix) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for ketorolac nasal spray (Sprix) and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained,

0 absent) MN criteria for ketorolac nasal spray (Sprix). (See Appendix B for full MN criteria.)

3. ***COMMITTEE ACTION: QUANTITY LIMITS***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 0 absent) restricting the maximum allowable quantity to 5 nasal spray bottles/30 days in the mail order pharmacy and retail network, which is consistent with the recommended dosing from the package labeling.

4. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD*** The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

E. Non-Insulin Diabetes Drugs: Dipeptidyl Dipeptidase-4 (DPP-4) Inhibitors—Sitagliptin/Metformin ER (Janumet XR) and Linagliptin/Metformin (Jentadueto)

Relative Clinical Effectiveness—Janumet XR and Jentadueto are fixed-dose combination products containing metformin in either an extended release (ER) formulation with sitagliptin (Janumet XR) or an immediate release (IR) formulation with linagliptin (Jentadueto). Sitagliptin is also available in a fixed-dose combination product with metformin IR (Janumet).

Both Janumet XR and Jentadueto were approved via the FDA 505(b)(2) process, requiring only proof of bioequivalence to their respective individual components. There are no efficacy studies with either agent. The combination of sitagliptin with metformin IR reduces hemoglobin A1c by 0.51% to 0.67%, while the combination of linagliptin with metformin IR decreases A1c by 0.4% to 0.5%. No studies evaluating clinical outcomes (e.g., cardiovascular death, myocardial infarction, and stroke) are available for the DPP-4 inhibitors, but trials are underway.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) there is no evidence to suggest either sitagliptin/ metformin ER (Janumet XR) or linagliptin/metformin (Jentadueto) have a compelling clinical advantage over the other DPP-4 inhibitor/metformin fixed-dose combinations included on the UF.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per day at all three POS was evaluated for sitagliptin/metformin ER (Janumet XR) and linagliptin/ metformin (Jentadueto) in relation to the other drugs in the DPP-4 inhibitors subclass. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that Janumet XR and Jentadueto were cost-effective when compared to other DPP-4 inhibitors included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (15 for, 0 opposed, 1 abstained, 1 absent) the following:

    - sitagliptin/metformin ER (Janumet XR) be designated step-preferred and formulary on the UF; and
    - linagliptin/metformin (Jentadueto) be designated non-preferred and formulary on the UF.
    - This recommendation includes step therapy, which requires a trial of sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/ simvastatin (Juvisync), or sitagliptin/metformin ER (Janumet XR) (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors also requires a trial of metformin or sulfonylurea for new patients.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee, recommended (14 for, 1 opposed, 1 abstained, 1 absent) sitagliptin/metformin ER (Janumet XR) be designated with BCF status, as sitagliptin-containing products have the majority of the current DPP-4 inhibitor utilization and are the most cost-effective agents.

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
   Existing automated prior authorization (step therapy) requires a trial of metformin or a sulfonylurea prior to use of a DPP-4 inhibitor. Additionally, sitagliptin-containing products (Januvia, Janumet, Janumet XR, and Juvisync) are the preferred agents in the DPP-4 inhibitors subclass. New users must try a preferred product before trying linagliptin or saxagliptin-containing products.

   The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria

    a) Automated PA criteria:

(1) The patient has filled a prescription for metformin or a sulfonylurea at any MHS pharmacy POS [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

(2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Janumet XR, Tradjenta, Jentadueto, Onglyza, or Kombiglyze XR) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria, if automated criteria are not met:

The fixed-dose combination product Janumet XR or Jentadueto is approved (eg, a trial of sulfonylurea is not required if):

(1) The patient has had an inadequate response to metformin or sulfonylurea.

(2) The patient has experienced the following adverse event while receiving a sulfonylurea: hypoglycemia requiring medical treatment.

(3) The patient has a contraindication to a sulfonylurea.

c) In addition to the above criteria regarding metformin and sulfonylurea, the following PA criteria would apply specifically to linagliptin/metformin metformin (Jentadueto):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENATION PERIOD***
The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is January 9, 2013.

V. UF DRUG CLASS REVIEWS

A. Anticoagulants—Heparin and Related Products

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Heparin and Related Products subclass of the anticoagulants. (The newer oral anticoagulants, including the Factor Xa inhibitors and direct thrombin inhibitors will be discussed at a later date.) The drugs in this subclass include unfractionated heparin, which is available in many generic formulations and will not be discussed further, enoxaparin (Lovenox), dalteparin (Fragmin), and fondaparinux (Arixtra). Two products, tinzaparin (Innohep) and ardeparin (Normiflow), were voluntarily discontinued by their manufacturers due to nonsafety reasons. The subclass has not previously been reviewed for UF placement. Generic biologic formulations of enoxaparin and fondaparinux are available; both are FDA AP-rated (therapeutically equivalent parenteral products) to Lovenox and Arixtra, respectively.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 2 absent) on the following clinical effectiveness conclusions:

- Enoxaparin has the widest clinical utility of the subclass, due to its long history of use, largest number of FDA-approved indications, availability in several dosage strengths, and recommendations by the American College of Chest Physicians for use in special populations (pregnancy, pediatrics). The package labeling cautions against use in patients with a history of heparin-induced thrombocytopenia (HIT).
- Fondaparinux has fewer FDA-approved indications than enoxaparin. It has a therapeutic niche for patients with a history of HIT. The risk of bleeding is increased in patients with low body weight (<50 kg), the elderly, and in patients with decreased renal function.
- The major limitation with dalteparin is the lack of an FDA-approved indication for treating deep venous thrombosis and pulmonary embolism. The package insert also cautions against use in patients with a history of HIT.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—Cost minimization (CMA) and budget impact analyses (BIA) were used to evaluate the drugs in this subclass, with corresponding sensitivity analyses. Due to recent availability of generic fondaparinux (Arixtra), an estimated generic drug price was used in the cost analyses. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that generic enoxaparin was the most cost-effective agent based on a weighted average cost per unit across all three POS, followed by branded dalteparin (Fragmin), and generic fondaparinux (ranked in order from most cost-effective to least cost-effective). BIA results showed that, among currently available formulary options, scenarios where generic enoxaparin is included on the BCF and dalteparin (Fragmin) and generic fondaparinux are included on the UF generated the greatest cost-avoidance projection.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (15 for, 0 opposed, 1 abstained, 1 absent) enoxaparin, dalteparin (Fragmin), and fondaparinux remain designated as formulary on the UF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) generic enoxaparin be designated with BCF status, based on clinical and cost effectivness. This clarifies the previous BCF listing for the low-molecular weight heparins stating that MTFs could choose between dalteparin (Fragmin), enoxaparin, or tinzaparin (Innohep). The BCF recommendation will be implemented upon signing of the minutes.

B. Androgens Anabolic Steroids—Transdermal and Buccal Testosterone Replacement Therapies

Background and Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the transdermal and buccal testosterone replacement therapies (TRTs), which are used for treating adult male hypogonadism. The TRT class is comprised of the following formulations of topical or buccal testosterone: transdermal patch (Androderm), transdermal 1% gel pump and gel packets (Androgel 1%), transdermal 1.62% gel pump (Androgel 1.62%), transdermal solution (Axiron), transdermal 2% gel pump (Fortesta), buccal tablets (Striant), and transdermal gel tubes (Testim).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the following concerning the TRT agents:

- Although high-quality comparative data is lacking, there appear to be no clinically relevant differences in efficacy between products.
- Transdermal and buccal testosterone replacement products effectively raise testosterone levels in hypogonadal men to the normal range when used in accordance with product labeling.
- Skin-to-skin transfer of transdermal testosterone to women and children should be minimized due to risk of virilization or premature onset of puberty. Testosterone buccal tablets (Striant) carry the lowest risk while the topically applied products carry the highest risk.
- Transdermal and buccal TRTs have a low overall incidence of systemic adverse events, which are not considered to differ clinically across products.

- The most frequent adverse events are dermal application site reactions for the transdermal products and oral application site reactions for buccal tablets; most are mild or transient in nature.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion
Pharmacoeconomic analyses were performed for the topical and buccal testosterone class, including CMA and BIA. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that transdermal 2% gel pump (Fortesta) was the least costly agent, followed by transdermal solution (Axiron), transdermal patch (Androderm), transdermal 1.62% gel pump (Androgel 1.62%), transdermal 1% gel pump and gel packets (Androgel 1%), transdermal gel tubes (Testim), and testosterone buccal tablets (Striant).

The analyses also evaluated the potential budgetary impact of cost scenarios where selected TRTs were designated with preferred product status (step therapy) on the UF; i.e., a trial of a preferred TRT would be required before using other TRTs. BIA results showed scenarios implementing step therapy were more cost-effective than scenarios without step therapy. The scenario where transdermal 2% gel (Fortesta) is step-preferred on the UF, all other TRTs are designated non-preferred on the UF or NF, and step therapy is applied to all current and new users of TRTs, was determined to be the most cost-effective scenario.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (13 for, 3 opposed, 1 abstained, 0 absent) the following scenario for the UF, which is the most clinically and cost-effective option for the MHS:
    - testosterone transdermal 2% gel pump (Fortesta) be designated step-preferred and formulary on the UF;
    - testosterone transdermal patch (Androderm), testosterone transdermal gel tubes (Testim), and testosterone buccal tablets (Striant) be designated non-preferred and formulary on the UF; and
    - testosterone transdermal 1% gel pump and gel packets (Androgel 1%), testosterone transdermal 1.62% gel pump (Androgel 1.62%), and testosterone transdermal solution (Axiron) be designated non-preferred and NF on the UF.
    - This recommendation includes step therapy, which requires a trial of testosterone transdermal 2% gel pump (Fortesta) prior to using other transdermal and buccal TRTs.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) testosterone transdermal 2% gel pump (Fortesta) be designated BCF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 4 absent) that the following manual PA criteria should apply to all current and new users of the testosterone replacement therapies. Coverage would be approved if the patient met any of the following criteria:

    a) Manual PA criteria for all transdermal and buccal testosterone replacement products:

        - Patient is male and has a diagnosis of hypogonadism evidenced by 2 or more morning testosterone levels in the presence of symptoms usually associated with hypogonadism;
        - Patient is a female and receiving testosterone for the following uses:
            - Treatment of hypoactive sexual desire in menopausal women (whether natural or surgical); or
            - Treatment of menopausal symptoms in women also receiving FDA-approved estrogen products (with or without concomitant progesterone).
            - Note that coverage of transdermal or buccal testosterone replacement therapies is not approved for osteoporosis or urinary incontinence.
            - Note that coverage for use in women will be by appeal only.
        - Note that use in adolescents under the age of 17 is not approved and will be by appeal only.

    b) In addition to the above criteria, the following PA criteria would apply specifically to transdermal gel tubes (Testim), transdermal patch (Androderm), buccal tablets (Striant), transdermal 1% gel pump and gel packets (Androgel 1%), transdermal 1.62% gel pump (Androgel 1.62%), and transdermal solution (Axiron):

        - The patient requires a testosterone replacement therapy that has a low risk of skin-to-skin transfer between family members (for Striant and Androderm only).

- The patient has tried transdermal 2% gel pump (Fortesta) for a minimum of 90 days AND failed to achieve total testosterone levels above 400ng/dL (lab must be drawn 2 hours after Fortesta application) AND denied improvement in symptoms.
- The patient has a contraindication or relative contraindication to Fortesta (e.g., hypersensitivity to a component [including alcohol]; concomitant disulfiram use) that does not apply to Testim, Androderm, Striant, Androgel 1%, Androgel 1.62%, or Axiron.
- The patient has experienced a clinically significant skin reaction to Fortesta that is not expected to occur with Testim, Androderm, Striant, Androgel 1%, Androgel 1.62%, or Axiron.

4. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluations for transdermal 1.62% gel pump (Androgel 1.62%), transdermal 1% gel pump and gel packets (Androgel 1%), the transdermal solution (Axiron), and the conditions for establishing MN for NF medications, the P&T Cominittee recommended (16 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Androgel 1.62%, Androgel 1%, and Axiron. (See Appendix B for full MN criteria.)

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is February 6, 2013.

VI. SECTION 703

A. Section 703—The P&T Committee reviewed a list of products—Amicar (branded aminocaproic acid), Kineret (anakinra), Phoslo (branded calcium acetate), Rheumatrex (branded methotrexate), Oxadrin (branded oxandrolone), Denavir (penciclovir), and Transderm-Scop (scopolamine patch)—to determine MN and pre-authorization criteria. These products were identified as not fulfilling refund requirements as required in section 703 of the 2008 National Defense Authorization Act. These drugs were made NF on the UF at previous P&T Committee meetings.

1. ***COMMITTEE ACTION: PRE-AUTHORIZATION CRITERIA***—The P&T Committee recommended (12 for, 0 opposed, 1 abstained, 4 absent) the following should apply to the drugs listed above. Coverage at retail network pharmacies would be approved if the patient met all the following criteria:

a) Manual Pre-Authorization Criteria:

(1) Obtaining the product from home delivery would be detrimental to the patient.

(2) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

The Pre-Authorization criteria listed above do not apply to any point of service other than retail network pharmacies.

VII. ITEMS FOR INFORMATION

A. Pharmacy Outcomes Research Team (PORT)—The PORT updated the P&T Committee on their various activities and research initiatives, and presented data on utilization patterns and effects of formulary changes in four drug classes:

- Antiplatelet agents—This class was reviewed in February 2012, with clopidogrel (Plavix) remaining on the BCF. A key element of the cost-effectiveness evaluation was the anticipated generic availability of clopidogrel. As of July 2012, generic clopidogrel accounted for more than 98% of all use in the retail network, accompanied by an approximately 72% decrease in the average cost per unit compared to April 2012. At least one clopidogrel generic formulation is available to MTFs under a Federal Supply Schedule contract. The P&T Committee acknowledged that MTFs may encounter delayed availability of clopidogrel generics through their prime vendors, but encouraged perseverance, given the volume of use and the potential for cost avoidance.
- Antilipidemics-1—An automated step therapy program/PA was implemented in October 2010, requiring use of the preferred statin agents (atorvastatin, lovastatin, pravastatin, simvastatin) prior to treatment with non-preferred agents (e.g., rosuvastatin, ezetimibe/simvastatin, etc). The P&T Committee noted that step therapy is working, as evidenced by a gradual decline in the use of non-preferred agents (particularly the lower dosage strengths) in the retail and mail POS, and the low percentage (<3%) of rejected claims under the step therapy program relative to total claims (paid claims plus rejected claims).
- Leukotriene Antagonists—A PA requirement for montelukast (Singulair) was implemented in March 2012. The PA allows for the treatment of asthma, but limits use for treatment of allergic rhinitis, unless the patient has failed or experienced an adverse event with nasal corticosteroids. The P&T Committee noted an overall decline in Singulair use, particularly in the retail and mail order POS. Additionally, there was no spike in usage in April 2012, which historically was noticeable and attributed to seasonal usage of Singulair, likely for allergic rhinitis. No information was available at the time of the meeting

concerning impact of the very recent generic approval of montelukast in August 2012.

- Phosphodiesterase-5 inhibitors for Erectile Dysfunction—In November 2011, sildenafil (Viagra) replaced vardenafil (Levitra) on the BCF (effective February 2012) and as the preferred agent under the existing step therapy/PA program (effective April 2012). MTFs are rapidly switching from Levitra to Viagra. It is too early to determine the full effect on relative market share of these agents at retail and mail.

B. TRICARE Formulary Search Tool—Information regarding updates to the TRICARE Formulary Search Tool was provided to the P&T Committee and is available at *http://pec.ha.osd.mil/formulary_search.php*.

VIII. ADJOURNMENT

The meeting adjourned at 1100 hours on August 16, 2012. The next meeting will be in November 2012.

Appendix A—Attendance: August 2012 P&T Committee Meeting

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary

Appendix D—Table of Abbreviations

Appendix A—Attendance: August 2012 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Carole Labadie, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG, via DCO	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
LTC Amy Young, MC for COL Ted Cieslak, MC	Army, Physician at Large
COL Michael Wynn, MC for LTC Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
COL Todd Williams, MS	Defense Medical Materiel Program Office
CDR Jay Peoloquin, MSC	Defense Logistics Agency Troop Support

Appendix A—Attendance (continued)

Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
CDR Matthew Baker, USPHS	Indian Health Service
Others Present	
LTC Chris Conrad, MS	DoD Pharmacoeconomic Center
Lt Col Melinda Henne, MC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez, USPHS	DoD Pharmacoeconomic Center
LCDR Joshua Devine, USPHS	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
LCDR Linh Quach, MSC	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Eugune Moore	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo via DCO	DoD Pharmacoeconomic Center
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
• Testosterone transdermal solution pump; 30 mg/actuation; (Axiron) • Testosterone 1%; 25 mg/2.5 gm, 50 mg/5 gm transdermal gel packets, and 12.5 mg /actuation gel pump (Androgel 1%) • Testosterone 1.62% transdermal gel pump; 20.25 mg/actuation (Androgel 1.62%) **Testosterone Replacement Therapies**	• Use of ALL formulary testosterone replacement products is contraindicated (e.g., due to hypersensitivity), and treatment with Axiron, Androgel 1%, or Androgel 1.62% is not contraindicated. • Patient has experienced or is likely to experience significant adverse effects from the formulary agents. • The formulary agents have resulted in therapeutic failure.
• Ibuprofen/famotidine (Duexis) **Non-steroidal Anti-Inflammatory Drugs (NSAIDS)**	• Use of formulary agents is contraindicated.
• Ketorolac nasal spray (Sprix) **Non-steroidal Anti-Inflammatory Drugs (NSAIDS)**	• Use of formulary agents is contraindicated. • The patient requires a nasal NSAID formulation and cannot take NSAIDs via any other route.
• Tafluprost ophthalmic solution (Zioptan) **Ophthalmic Prostaglandins**	• The use of formulary alternatives is contraindicated. • The patient has experienced or is likely to experience significant adverse effects from the formulary agents.
• Abatacept SQ (Orencia) **Targeted Immunomodulatory Biologics (TIBs)**	• The use of formulary alternatives is contraindicated. • The patient has experienced or is likely to experience significant adverse effects from the formulary agents. • The formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to a non-formulary agent, and changing to a formulary agent would incur unacceptable risk. • The patient is currently receiving abatacept IV and is switching to abatacept SQ.

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2012	**Testosterone Replacement Therapies** **Topical and Buccal products subclass**	UF Review	• testosterone transdermal 2% gel pump; 10 mg/actuation (Fortesta)	• testosterone 50 mg/5 gm transdermal gel tubes (Testim) • testosterone 2 mg/24 hr, 4 mg/24 hr transdermal patches (Androderm) • testosterone 30 mg buccal tablets (Striant)	• testosterone transdermal solution pump; 30 mg/actuation; (Axiron) • testosterone 1%; 25 mg/2.5 gm, 50 mg/ 5 gm transdermal gel packets, and 12.5 mg/ actuation gel pump (Androgel 1%) • testosterone 1.62% transdermal gel pump; 20.25 mg/actuation (Androgel 1.62%)	Pending signing of minutes/ 90 days	PA required; see Comments	• All current and new users of topical and buccal testosterone replacement products must go through the PA process to ensure diagnosis of hypogonadism • Fortesta 2% gel pump is the preferred product; all users of topical and buccal testosterone replacement products must have trial of Fortesta 2% gel prior to other products
Aug 2012	**Anticoagulants** **Heparin and related products subclass**	UF Review	• enoxaparin (generic)	• dalteparin (Fragmin) • fondaparinux (generic)	• Not applicable (no products designated as nonformulary)	Pending signing of minutes	-	• enoxaparin generic designated BCF

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2012	**Non-Steroidal Anti-inflammatory Drugs** Previous review: Aug 2011	New Drugs in Already Reviewed Classes Ibuprofen/ famotidine (Duexis) Ketorolac nasal spray (Sprix)	• ibuprofen 400 mg, 600 mg & 800 mg (generic) • indomethacin 25 mg & 50 mg (generic) • meloxicam 7.5 mg & 15 mg (generic) • naproxen 250 mg & 500 mg & 125 mg/5 mL susp (generic)	• celecoxib (Celebrex) • diclofenac/misoprostol (Arthrotec) • diclofenac potassium tablets (Cataflam generic) • diclofenac sodium tablets (Voltaren generic) • diflunisal • etodolac • fenoprofen • flurbiprofen • ketoprofen • ketorolac • meclofenamate • nabumetone • naproxen sodium 275 mg & 550 mg (Anaprox, generic) • oxaprozin • piroxicam • sulindac • tolmetin • naproxen/esomeprazole (Vimovo)	*August 2012* • **ibuprofen/famotidine (Duexis)** • **ketorolac nasal spray (Sprix)** *August 2011* • diclofenac potassium liquid-filled capsules (Zipsor) 25 mg • diclofenac potassium powder packets 50 mg (Cambia) • naproxen sodium ER (Naprelan CR, generic) 375 mg, 500 mg, & 750 mg ER tabs, dosing card • mefenamic acid (Ponstel, generic) 250 mg	Pending signing of minutes/ 60 days	Quantity Limits for ketorolac nasal spray (Sprix): 5 bottles for 30-day supply in both the Retail Network and Mail Order Pharmacy	• ibuprofen/ famotidine (Duexis) designated nonformulary • ketoralac nasal spray (Sprix) designated nonformulary
Aug 2012	**Glaucoma Agents** **Ophthalmic Prostaglandin Subclass** Previous review: Aug 2011	New Drug in Already Reviewed Class Tafluprost (Zioptan)	• latanoprost (generic)	• bimatoprost (Lumigan)	*August 2012* • **tafluprost (Zioptan)** *February 2007* • travoprost (Travatan Z)	Pending signing of minutes/ 60 days	-	• tafluprost (Zioptan) designated nonformulary
Aug 2012	**Non-Insulin Diabetes Drugs** **DPP-4 Inhibitors Subclass** Previous reviews: Feb 2012 and Nov 2012	New Drug in Already Reviewed Class sitagliptin/ metformin ER (Janumet XR) linagliptin/ metformin IR (Jentadueto)	*August 2012* • **sitagliptin/ metformin ER (Janumet XR)** *Feb 2012* • sitagliptin (Januvia) • sitagliptin/metformin (Janumet)	*August 2012* • **linagliptin/metformin IR (Jentadueto)** *February 2012* • sitagliptin/Simvastatin (Juvisync) • linagliptin (Tradjenta)	*February 2012* • saxagliptin (Onglyza) • saxagliptin/metformin ER (Kombiglyze XR)	Pending signing of minutes/ 60 days	Step therapy required – see comments	• Must try metformin and sulfonylurea 1st before any DPP-4 drug • Must try sitagliptin-containing product 1st before Tradjenta, Jentadueto, Onglyza, or Kombiglyze XR

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2012	**Targeted Immuno-modulatory Biologics** Previous review: Nov 2007	New Drug in Already Reviewed Class abatacept SQ (Orencia SC)	• adalimumab SQ (Humira)	• alefacept (Amevive)	*August 2012* • **abatacept SQ (Orencia)** *Nov 2007 and Aug 2009* • etanercept (Enbrel) (etanercept) • anakinra (Kineret) • certolizumab (Cimzia) • golimumab (Simponi)	60 days	• PA limiting use to FDA-approved indications was approved in Nov 2011 • QLs approved in Nov 2011 • Retail: 4 syringes/28 days • Mail Order: 8 syringes/56 days	• abatacept SQ (Orencia) designated nonformulary • adalimumab (Humira) is the formulary alternative for treating rheumatoid arthritis

* TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix D—Table of Abbreviations

BCF	Basic Core Formulary
BIA	budget impact analysis
C.F.R.	Code of Federal Regulations
CMA	cost minimization analysis
DoD	Department of Defense
DPP-4	dipeptidyl dipeptidase-4
ECF	Extended Core Formulary
ER	extended release
FDA	U.S. Food and Drug Administration
FR	Federal Register
GI	gastrointestinal
HIT	heparin-induced thrombocytopenia
IOP	intraocular pressure
IR	immediate release
IV	intravenous
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
NF	nonformulary
NSAIDs	non-steroidal anti-inflammatory drugs
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
RA	rheumatoid arthritis
SC	subcutaneous
TIBs	targeted immunomodulatory biologics
TNF	tumor necrosis factor
TRTs	transdermal and buccal testosterone replacement therapies
UF	Uniform Formulary
U.S.C.	United States Code
VA	U.S. Department of Veterans Affairs

DECISION PAPER

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2012

I. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Gabapentin enacarbil (Horizant) and gabapentin (Gralise)

Relative clinical effectiveness conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) the following: gabapentin enacarbil (Horizant) and gabapentin (Gralise) are once-daily formulations of gabapentin (Neurontin, generics). There is no evidence to suggest either drug has a compelling clinical advantage over the other drugs for non-opioid pain syndromes included on the Uniform Formulary (UF).

Relative cost- effectiveness conclusion (15 for, 0 opposed, 0 abstained, 0 absent) Gabapentin enacarbil (Horizant) and gabapentin (Gralise) were not cost-effective when compared to other non-opioid pain syndrome agents included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (14 for, 0 opposed, 1 abstained, 0 absent) gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated nonformulary (NF) due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***
Existing step therapy/PA requires a trial of generic gabapentin prior to pregabalin (Lyrica) in new users. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) that both gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated non-step-preferred, requiring a trial of generic gabapentin in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

   a) Automated PA criteria: The patient has filled a prescription for gabapentin at any Military Health System (MHS) pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

   b) Manual PA criteria: The patient has a contraindication to or experienced adverse events with gabapentin or the formulary non-opioid pain syndrome agents which is not expected to occur with Horizant or Gralise.

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following MN criteria for Horizant and Gralise: the patient has a contraindication to or has experienced an adverse effect from gabapentin or the formulary non-opioid pain syndrome agents.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all points of service (POS), and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is September 19, 2012.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

II. UNIFORM FORMULARY DRUG CLASS REVIEWS

Relative clinical effectiveness conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) the newer sedative hypnotic agents all improve sleep latency (onset) compared to placebo. Sleep maintenance is improved with zolpidem IR (Ambien, generic), zolpidem CR (Ambien CR, generic), eszopiclone (Lunesta), and doxepin (Silenor). Based on an indirect comparison, there do not appear to be clinically relevant differences between zolpidem CR and Lunesta in terms of objective sleep measures.

Relative cost effectiveness conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) zolpidem IR was the least costly agent, followed by zaleplon, zolpidem CR, eszopiclone (Lunesta), doxepin (Silenor), zolpidem SL (Edluar), and ramelteon (Rozerem). BIA results showed minimal differences between scenarios, but the projected budgetary impact in the MHS did vary depending on market movement of zolpidem CR when designated step-preferred versus non-step-preferred, rate of price decline of generic zolpidem CR, and market migration of generic drugs versus branded products

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 1 opposed, 2 abstained, 0 absent) the following scenario for the UF, which includes a drug for sleep onset (zolpidem IR), a drug for sleep maintenance (zolpidem CR and Lunesta), and a non-controlled drug (Silenor), and is the most cost-effective option for the MHS:

- zolpidem IR and zaleplon be designated formulary on the UF and step-preferred. This recommendation incorporates step therapy, which requires a trial of zolpidem IR or zaleplon (step-preferred drugs) in new users before use of another newer sedative hypnotic drug;
- zolpidem CR, doxepin (Silenor), and eszopiclone (Lunesta) be designated formulary on the UF and non-step-preferred;
- ramelteon (Rozerem) and zolpidem SL (Edluar) remain NF and non-step-preferred (behind the step);
- zolpidem oral spray (Zolpimist) is not covered by a written agreement by the manufacturer to honor the pricing standards required by 10 United States Code 1074g(f). Pursuant to 32 Code of Federal Regulations (C.F.R.) 199.21(q)(2)(A), Zolpimist is designated NF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) zolpidem IR maintain BCF status on the UF.

3. ***COMMITTEE ACTION: PA CRITERIA***—Existing step therapy/PA requires a trial of generic zolpidem IR prior to the other newer sedative hypnotics in new users. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to the newer sedative hypnotics drug class. Coverage would be approved if the patient met any of the following criteria:
   a) Automated PA criteria: The patient has filled a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
   b) Manual PA criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

4. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) retaining the current MN criteria for zolpidem SL (Edluar) and ramelteon (Rozerem): the patient has had an inadequate response to, been unable to tolerate due to adverse effects, or has contraindications to zolpidem IR or zaleplon, or there is no alternative formulary agent.

5. ***COMMITTEE ACTION: PRE-AUTHORIZATION AND MN CRITERIA FOR ZOLPIDEM ORAL SPRAY (ZOLPIMIST)***—Pursuant to 32 Code of Federal Regulations (C.F.R.) 199.21(q)(2)(B), the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following pre-authorization criteria should apply to availability of Zolpimist through retail network pharmacies. Coverage at retail network pharmacies would be approved if the patient met any of the following criteria:

   a) Manual Pre-Authorization Criteria:

      (1) Use of the formulary agent is contraindicated.

      (2) Obtaining the product for home delivery would be detrimental to the patient.

   The PA criteria listed above do not apply to any point of service other than retail network pharmacies.

   (b) Medical Necessity Criteria:

      (1) Use of the formulary agent is contraindicated.

COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is October 17, 2012.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

All recommended actions pertaining to Zolpimist are to be held in abeyance until verification is received from the Department of Veterans Affairs that Zolpimist is a covered drug under the Veterans Health Care Act.

III. SPECIAL PROGRAMS

A. Smoking Cessation Program

Background Relative Clinical Effectiveness—Drugs for smoking cessation [varenicline (Chantix), bupropion SR 150 mg (Zyban), and nicotine patch, gum, lozenge, nasal spray (Nicotrol NS), and inhaler (Nicotrol)] are currently excluded from the TRICARE® benefit by regulation (32 C.F.R 199.4(g)(65)). The Duncan Hunter National Defense Authorization Act for Fiscal Year 2009 requires the availability, at no cost to the beneficiary, of pharmaceuticals used for smoking cessation to select

beneficiary groups with a limitation on the availability of such pharmaceuticals to the national mail order pharmacy program under the TRICARE program if appropriate. The Proposed Rule, which provides that smoking cessation pharmaceutical agents, including FDA-approved over-the-counter pharmaceutical agents, are available through the TRICARE Mail Order Pharmacy or the MTF, has been published in the Federal Register (76 FR 58199), comments have been received, and the Final Rule is pending publication.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) the following: varenicline (Chantix), bupropion SR, and nicotine replacement therapy (NRT) are efficacious versus placebo for improving long-term smoking abstinence. Combination therapy, in particular nicotine patch plus gum, is more efficacious than monotherapy. Varenicline (Chantix) is the most efficacious monotherapy for smoking cessation. Safety concerns exist with varenicline, including adverse neuropsychiatric effects (behavioral changes, agitation, suicide/suicidal ideation, and depression). In patients with pre-existing stable cardiovascular (CV) disease, generally the benefit of abstinence outweighs the increased adverse CV risk with varenicline. Local MTFs remain at liberty to design their own smoking cessation program, defining which elements will be included in that program.

Relative Cost-Effectiveness Analysis and Conclusion—The P&T Committee concluded (15 for, 0 against, 0 abstained, 0 absent) the following:

- Cost-minimization results showed that nicotine patch and gum were the least costly products among the NRTs, and bupropion SR was the least costly non-NRT option.
- Cost-effectiveness analyses results demonstrated that, in adult patients who smoke more than 10 cigarettes a day, combination therapy (nicotine patch plus gum) was the most cost-effective treatment for tobacco dependence offering the greatest improvement in rates of long-term smoking abstinence. Although less cost-effective than combination therapy, varenicline was recognized as a cost-effective option when evaluating abstinence rates with monotherapy.
- Budget impact analysis showed inclusion of all 7 smoking cessation products in the Smoking Cessation Programs was the most favorable scenario for the MHS.

1. ***COMMITTEE ACTION: COVERAGE RECOMMENDATION***—The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) varenicline (Chantix), bupropion SR 150 mg, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) be covered agents in the TRICARE Smoking Cessation Program, contingent on publication of the Final Rule. This coverage recommendation allows for several treatment modalities to

accommodate patient preference and provide optimal access and opportunity for successful abstinence. No smoking cessation drugs were recommended to be excluded from the program.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) bupropion SR 150 mg; nicotine patch 7 mg, 14 mg, and 21 mg; and, nicotine gum 2 mg and 4 mg be designated BCF on the UF, contingent on publication of the Final Rule.

3. ***COMMITTEE ACTION: VARENICLINE PA***—The P&T Committee rejected (6 in favor of prior authorization for varenicline, 8 opposed, 1 abstained, 0 absent) the proposal that PA criteria should apply to varenicline (Chantix). PA criteria for varenicline were proposed for safety concerns, primarily neuropsychiatric AEs. While the P&T Committee recognized the potential for safety concerns with varenicline, they also concluded that a PA was not required to ensure safe prescribing with the medication because the risks with varenicline are understood by prescribing providers and can be successfully managed without PA criteria.

4. ***COMMITTEE ACTION: COVERED BENEFICIARY CRITERIA AND PA FOR A 3rd QUIT ATTEMPT***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following coverage criteria should apply to all seven smoking cessation products [varenicline (Chantix), bupropion SR 150 mg, nicotine gum, patch, lozenge, nasal spray, and inhaler)], consistent with the requirements in the Proposed Rule, and contingent on publication of the Final Rule. Coverage not approved for patients under the age of 18 or for Medicare-eligible beneficiaries. Coverage for a 3rd quit attempt within one year may be pre-approved if the provider has verified that the patient would benefit from a 3rd quit attempt.

5. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (14 for, 0 opposed, 1 abstain, 0 absent) QLs/days supply limits, restricting the maximum allowable smoking cessation quantity to a 60-day supply per claim at the TRICARE Mail Order POS, with a maximum 240-day supply per rolling 365-day period. Additionally, nicotine gum and nicotine lozenge would be limited to 300 pieces per 60-day claim, rounded to the nearest multiple of the package size (e.g., boxes of 75 or 100). The QL recommendations are contingent on publication of the Final Rule.

6. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in the MTF and mail order POS, following publication of the Final Rule.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

August 8, 2012
Date

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE MINUTES AND RECOMMENDATIONS

May 2012

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 16, 2012, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of November Minutes**—Jonathon Woodson M.D., Director, approved the minutes for the February 2012 DoD P&T Committee meeting on May 7, 2012. A 6–12 month follow-up of safety for tapentadol ER (Nucynta ER) was requested by the Director.
2. **Correction of November 2011 Minutes—BCF Clarification for Short-Acting Beta Agonists:** The August 2011 P&T Committee minutes were clarified to state the Basic Core Formulary (BCF) listing for nebulized albuterol is the 0.083% 2.5 mg/3 mL formulation—not the 0.5% 2.5 mg/5mL vial—for the short-acting beta agonists.
3. **Correction of August 2011 Minutes—Prior Authorization (PA) Implementation Date for Singulair:** The PA implementation date for montelukast (Singulair) was changed from February 1, 2012, to March 21, 2012.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations (C.F.R.) 199.21(e)(1). All Uniform Formulary (UF) and BCF recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Gabapentin enacarbil (Horizant) and gabapentin (Gralise)

Relative Clinical Effectiveness—Gabapentin enacarbil (Horizant) and gabapentin (Gralise) are once-daily formulations of gabapentin (Neurontin, generics). At the time of the May 2012 meeting, Horizant was FDA-approved for treating restless leg syndrome (RLS), but was undergoing FDA review for post-herpetic neuralgia. The Depression/Non-opioid Pain Syndrome Drug Class was reviewed for UF status at the November 2011 DoD P&T Committee meeting. Gabapentin (Neurontin, generics) is currently on the BCF. Step therapy/PA requires a trial of generic gabapentin prior to pregabalin (Lyrica) in new users.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) for both Horizant and Gralise, although the two drugs are dosed once daily versus multiple daily dosing required with generic gabapentin, there is no evidence to suggest either drug has a compelling clinical advantage over the other drugs for non-opioid pain syndromes included on the UF. Dosing conversion guidelines between Horizant, Gralise, and generic gabapentin are not available and these agents are not interchangeable due to differing pharmacokinetic properties. Gralise requires a large tablet burden to reach recommended dosing. Both drugs may cause significant somnolence and sedation, and Horizant carries a warning for adversely impairing driving ability.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—A pharmacoeconomic analysis was performed. The weighted average cost per day at all three points of service (POS) was evaluated for gabapentin enacarbil (Horizant) and gabapentin (Gralise) in relation to the other drugs for non-opioid pain syndromes. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that Horizant and Gralise were not cost-effective when compared to other non-opioid pain syndrome agents included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee, recommended (14 for, 0 opposed, 1 abstained, 0 absent) gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

2. ***COMMITTEE ACTION: GABAPENTIN ENACARBIL (HORIZANT) AND GABAPENTIN (GRALISE) PA CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) that both gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated non-step-preferred, requiring a trial of generic gabapentin in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

    a) Automated PA criteria:

(1) The patient has filled a prescription for gabapentin at any Military Health System (MHS) pharmacy POS [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

b) Manual (paper) PA criteria, if automated criteria are not met:

(1) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

(2) The patient has experienced adverse events (AEs) with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

3. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following MN criteria for Horizant and Gralise:

a) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents.

b) The patient has experienced AE with gabapentin or the formulary non-opioid pain syndrome agents.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is September 19, 2012

V. UF DRUG CLASS REVIEWS

A. Newer Sedative Hypnotics Drugs

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Newer Sedative Hypnotics (SED-1s), which are used for treating insomnia. The SED-1s class is comprised of the following: zolpidem

immediate-release (IR) (Ambien; generics), zolpidem extended-release (CR) (Ambien CR; generics), zolpidem oral spray (Zolpimist), zolpidem sublingual (SL) (Edluar), eszopiclone (Lunesta), zaleplon (Sonata; generics), ramelteon (Rozerem), and doxepin (Silenor).

A step therapy/PA requirement has been in effect for the SED-1s class since August 2007, requiring that new SED-1s users try the preferred agent, zolpidem IR, before TRICARE® will cover the other agents in this drug class.

Zolpidem oral spray (Zolpimist) is not covered by a written agreement by the manufacturer to honor the pricing standards required by 10 United States Code (U.S.C.) 1074g(f).

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions:

- The SED-1s all improve sleep latency (onset) compared to placebo. Sleep maintenance is improved with zolpidem IR, zolpidem CR, eszopiclone, and doxepin.
- Based on an indirect comparison, there do not appear to be clinically relevant differences between zolpidem CR and eszopiclone in terms of objective sleep measures.
- Doxepin improves insomnia by improving sleep maintenance; no comparative data exists with other drugs in the class.
- Zolpidem oral spray does not have comparative clinical trials with other SED-1s. FDA approval was granted based on the data originally submitted with Ambien. Zolpimist may pose additional risk for abuse given its dosage form.
- A recently published trial (Kripke, 2012) documented an increased risk of death with insomnia drugs. The interpretation of the results is hampered by several limitations in study design. No further recommendations regarding sedative hypnotic drug prescribing can be made at this time.
- The potential for abuse/misuse exists with the newer sedative hypnotics, with the exception of ramelteon and doxepin.
- The Pharmacy Outcomes Research Team (PORT) presented the results of several analyses assessing the outcomes of step therapy over the last four years. There was a decline in the number of step therapy rejections over time and an increase in utilization of the preferred product, zolpidem IR, suggesting that prescribers were aware of the step therapy requirement. The step therapy requirement did not move market share away from the MTFs, as 26% of the zolpidem IR prescriptions originated from civilian providers.

Relative Cost-Effectiveness Analysis and Conclusion—Pharmacoeconomic analyses were performed for the SED-1s class, including cost minimization analysis (CMA) and budget impact analyses (BIA). The P&T Committee concluded (15 for, 0 against, 0 abstained, 0 absent) zolpidem IR was the least costly agent, followed by zaleplon, zolpidem CR, eszopiclone (Lunesta), doxepin (Silenor), zolpidem SL (Edluar), and ramelteon (Rozerem). BIA results showed minimal differences between scenarios, but the projected budgetary impact in the MHS did vary depending on market movement of zolpidem CR when designated step-preferred versus non-step-preferred, rate of price decline of generic zolpidem CR, and market migration of generic drugs versus branded products.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—The P&T Committee recommended (12 for, 1 opposed, 2 abstained, 0 absent) the following:

    - zolpidem IR and zaleplon be designated formulary on the UF and step-preferred. This recommendation incorporates step therapy, which requires a trial of zolpidem IR or zaleplon (step-preferred drugs) in new users before use of another SED-1s drug;
    - zolpidem CR, doxepin (Silenor), and eszopiclone (Lunesta) be designated formulary on the UF and non-step-preferred;
    - ramelteon (Rozerem) and zolpidem SL (Edluar) remain NF and non-step-preferred (behind the step);
    - zolpidem oral spray (Zolpimist) is not covered by a written agreement by the manufacturer to honor the pricing standards required by 10 United States Code 1074g(f). Pursuant to 32 Code of Federal Regulations (C.F.R.) 199.21(q)(2)(A), Zolpimist is designated NF.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) zolpidem IR maintain BCF status on the UF.

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to the SED-1s class. Coverage would be approved if the patient met any of the following criteria:

    a) Automated PA criteria: The patient has received a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

    b) Manual (paper) PA criteria, if automated criteria are not met: The patient has had an inadequate response to, been unable to tolerate due to adverse

effects, or has contraindications to zolpidem IR or zaleplon (e.g., hypersensitivity, aberrant behaviors, or intolerable rebound insomnia).

4. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) retaining the current MN criteria for zolpidem SL (Edluar) and ramelteon (Rozerem):

   a) The patient has had an inadequate response to, been unable to tolerate due to adverse effects, or has contraindications to zolpidem IR or zaleplon (e.g., hypersensitivity, aberrant behaviors, or intolerable rebound insomnia).

   b) There is no alternative formulary agent. For zolpidem SL (Edluar), the patient is unable to swallow or has swallowing difficulties. For ramelteon (Rozerem), patient requires a non-controlled agent due to potential for abuse and cannot take doxepin (Silenor).

5. ***COMMITTEE ACTION: PRE-AUTHORIZATION AND MN CRITERIA FOR ZOLPIDEM ORAL SPRAY (ZOLPIMIST)***—Pursuant to 32 Code of Federal Regulations (C.F.R.) 199.21(q)(2)(B), the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following pre-authorization criteria should apply to availability of Zolpimist through retail network pharmacies. Coverage at retail network pharmacies would be approved if the patient met any of the following criteria:

   a) Manual Pre-Authorization Criteria:

      (1) Use of the formulary agent is contraindicated.

      (2) Obtaining the product for home delivery would be detrimental to the patient.

   The PA criteria listed above do not apply to any point of service other than retail network pharmacies.

   (b) Medical Necessity Criteria:

      (1) Use of the formulary agent is contraindicated.

6. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD*** The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS. Based on the P&T Committee's recommendation, the effective date is October 17, 2012.

VI. SPECIAL PROGRAM REVIEW

A. Smoking Cessation Program

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the FDA-approved agents for smoking cessation. These agents include: varenicline (Chantix), bupropion SR 150 mg (Zyban), and nicotine, provided in five unique routes of administration (patch, gum, lozenge, nasal spray, and inhaler). Nicotine, via the patch, gum, and lozenge are available over-the-counter but are considered for coverage, by prescription, as part of this program.

Presently, the smoking cessation agents are not part of the TRICARE benefit, but are provided locally at most MTFs. The P&T Committee has not previously reviewed the smoking cessation drugs, as they were excluded from the TRICARE benefit by regulation (32 C.F.R. 199.4(g)(65)). The Duncan Hunter National Defense Authorization Act for Fiscal Year 2009 requires the availability, at no cost to the beneficiary, of pharmaceuticals used for smoking cessation to select beneficiary groups with a limitation on the availability of such pharmaceuticals to the national mail order pharmacy program under the TRICARE program if appropriate. The Proposed Rule has been published in the Federal Register (76 FR 58199), comments have been received, and the Final Rule is pending publication.

The Proposed Rule would limit coverage of smoking cessation products to the MTFs and TRICARE Mail Order Pharmacy POS, and to select beneficiary groups. The Proposed Rule allows two quit attempts, defined as 120-day periods, to be available annually to eligible beneficiaries. Medication coverage for a third attempt may be offered with prior authorization.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

- Varenicline (Chantix), bupropion SR, and nicotine replacement therapy (NRT) are efficacious versus placebo for improving long-term smoking abstinence. There is additive efficacy when the smoking cessation drugs are combined with behavioral therapy.
- For combination therapy, nicotine patch plus gum or nasal spray is the most efficacious smoking cessation therapy. Use of the nasal spray is limited by poor tolerability.
- Varenicline (Chantix) is the most efficacious monotherapy for smoking cessation.
- Safety concerns exist for varenicline (Chantix). Although the available data has limitations in study design and shows conflicting results, overall there appears to

be an association between varenicline and adverse neuropsychiatric events to include behavioral changes, agitation, suicide/suicidal ideation, and depression.

- Caution should be exercised if varenicline is prescribed to patients with active psychiatric comorbidities.
- Varenicline has shown efficacy in patients with cardiovascular (CV) disease and chronic obstructive pulmonary disease. There is conflicting data as to whether varenicline is associated with a higher risk of adverse CV events, including non-fatal myocardial infarction, need for coronary revascularization, hospitalization for angina, and peripheral vascular disease. However, the benefits of smoking cessation with varenicline are felt to outweigh the risks in patients with pre-existing, stable CV disease.
- Varenicline is more efficacious in terms of abstinence at 52 weeks than bupropion SR. Bupropion SR is more efficacious than the NRT patch. There is additive efficacy if bupropion SR is added on to NRT (either gum or patch). However, the combination is no better than bupropion monotherapy if the bupropion is initiated first.
- When varenicline is compared to bupropion SR in randomized, controlled trials, the most commonly reported AEs are nausea (29%), insomnia (14%), abnormal dreams (13%), and headache (13%). The most common AEs with bupropion include insomnia (21%), nausea (7%), and dry mouth (10%).
- Bupropion carries a black box warning for changes in behavior, depressed mood, hostility, and suicidal ideation.
- All smoking cessation drugs show poor rates of compliance in both effectiveness and efficacy trials. Patient preference for a particular medication modality will determine compliance. Long-term abstinence may occur in cases of incomplete compliance. The typical long-term abstainer will make four or more serious quit attempts before finding success.
- Local MTFs remain at liberty to design their own smoking cessation program, defining which elements will be included in that program.

Relative Cost-Effectiveness Analysis and Conclusion—CMA and cost-effectiveness analyses (CEAs) were used to compare the different treatment options for smoking cessation, as efficacy and safety differences between the agents were noted in the clinical review. BIA was also performed to compare several program scenarios. The P&T Committee concluded (15 for, 0 against, 0 abstained, 0 absent) the following:

- CMA results showed that nicotine patch and gum were the least costly products among available NRTs, and bupropion SR was the least costly non-NRT option.

- CEA results demonstrated that, in adult patients who smoke more than 10 cigarettes a day, combination therapy (nicotine patch plus gum) was the most cost-effective treatment for tobacco dependence offering the greatest improvement in rates of long-term smoking abstinence. Although less cost-effective than combination therapy, varenicline was recognized as a cost-effective option when evaluating abstinence rates with monotherapy.
- BIA results showed that inclusion of bupropion SR, varenicline, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) in the TRICARE Smoking Cessation Program was the most favorable scenario for the MHS.

1. ***COMMITTEE ACTION: COVERAGE RECOMMENDATION***—The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) varenicline (Chantix), bupropion SR 150 mg, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) be covered agents in the TRICARE Smoking Cessation Program, contingent on publication of the Final Rule. No smoking cessation drugs were recommended to be excluded from the program.

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) bupropion SR 150 mg; nicotine patch 7 mg, 14 mg, and 21 mg; and, nicotine gum 2 mg and 4 mg be designated BCF on the UF, contingent on publication of the Final Rule.

3. ***COMMITTEE ACTION: VARENICLINE PA***—The P&T Committee rejected (6 in favor of prior authorization for varenicline, 8 opposed, 1 abstained, 0 absent) the proposal that PA criteria should apply to varenicline (Chantix). PA criteria for varenicline were proposed for safety concerns, primarily neuropsychiatric AEs. While the P&T Committee recognized the potential for safety concerns with varenicline, they also concluded that a PA was not required to ensure safe prescribing with the medication because the risks with varenicline are understood by prescribing providers and can be successfully managed without PA criteria.

4. ***COMMITTEE ACTION: COVERED BENEFICIARY CRITERIA AND PA FOR A 3rd QUIT ATTEMPT***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following coverage criteria should apply to all seven smoking cessation products [varenicline (Chantix), buproprion SR 150 mg, nicotine gum, patch, lozenge, nasal spray, and inhaler], consistent with the requirements in the Proposed Rule, and contingent on publication of the Final Rule. Coverage not approved for patients under the age of 18 or for Medicare-eligible beneficiaries. Coverage for a 3rd quit attempt within one year may be

pre-approved if the provider has verified that the patient would benefit from a 3rd quit attempt.

5. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (14 for, 0 opposed, 1 abstain, 0 absent) QLs/days supply limits, restricting the maximum allowable smoking cessation quantity to a 60-day supply per claim at the TRICARE Mail Order POS, with a maximum 240-day supply per rolling 365-day period. Additionally, nicotine gum and nicotine lozenge would be limited to 300 pieces per 60-day claim, rounded to the nearest multiple of the package size (e.g., boxes of 75 or 100). The QL recommendations are contingent on publication of the Final Rule.

6. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in the MTF and mail order POS, following publication of the Final Rule.

VII. ITEMS FOR INFORMATION

A. Weight Loss Drugs Update—Currently C.F.R. 199.4 states that weight loss control medications are not a covered TRICARE pharmacy benefit. A brief overview of weight loss medications was provided, due to increasing awareness by the White House of the childhood obesity epidemic and recent actions by the FDA Endocrinologic and Metabolic Drugs Advisory Committee, which recommended three investigational weight loss drugs for approval. The P&T Committee will review the clinical and cost-effectiveness of the weight loss drugs if the regulation changes.

B. Non-approved drugs—The P&T Committee was briefed on the dispensing of non-FDA-approved drugs from the retail POS and the C.F.R. requirements for TRICARE coverage of prescription medications. Recommendations were made to develop an internal process to identify and review nonapproved products, determine the beneficiary impact of excluding these products, and work with the retail network contractor to potentially exclude coverage of these nonapproved products.

C. Compounded Medications under the TRICARE Benefit—The P&T Committee was briefed on compounded medications dispensed from the retail and mail order POS. MHS expenditures for compounded medications are significant and increasing, and compounded medications have a high potential for inappropriate use. Further updates and initiatives in the area of compounded medications will be provided to the P&T Committee.

D. PORT—The PORT provided the P&T Committee with an update and review of findings on various topics.

E. **Prescription Omega-3-Acid Esters (Lovaza) PA Update**—An update on the results of the PA for Lovaza was provided. Since implementation of the PA in July 2011, there was an initial steep decline in the numbers of Lovaza prescriptions filled, which has stabilized.

F. **Renin Angiotension Antihypertensive Agents (RAAs) PA Update**—The P&T Committee was briefed on recent developments in the RAAs class. Two products are now available in generic formulations, eprosartan (Teveten) and irbesartan (Avapro). No recommendations were made to change the existing step therapy/PA. The class is slated for re-review following generic availability of additional proprietary products and publication of updated hypertension guidelines from the National Heart Lung and Blood Institute.

VIII. ADJOURNMENT

The meeting adjourned at 1645 hours on May 16, 2012. The next meeting will be in August 2012.

Appendix A—Attendance: May 2012 P&T Committee Meeting

Appendix B—Table of Implementation Status of UF Recommendations/Decisions

Appendix C—Table of Abbreviations

Appendix A—Attendance: May 2012 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
LTC Ricardo Nannini, MSC for COL Carole Labadie, MSC	Army, Pharmacy Officer
Col David Bobb, BSC for Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson, USCG	Coast Guard, Pharmacy Officer
CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
LCDR Tiffany Scott	Defense Logistics Agency Troop Support
Guests	
Mr. Bill Davies via DCO	TRICARE Management Activity, Pharmaceutical Operations Directorate
Donna Oetama	University of Incarnate Word, Feik School of Pharmacy
Tuyet Pham	University of Incarnate Word, Feik School of Pharmacy
Kathy Uriarte	University of Incarnate Word, Feik School of Pharmacy

Appendix A—Attendance: May 2012 P&T Committee Meeting (continued)

Guests	
Tina Christi Lopez	University of Incarnate Word, Feik School of Pharmacy
Others Present	
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe via DCO	DoD Pharmacoeconomic Center
LCDR Joshua Devine	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Bradley Clarkson	Pharmacy Resident
Lt Kellye Donovan	Pharmacy Resident

Appendix B—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2012	**Smoking Cessation Program**	Program Review	**Nicotine Products** OTC Nicotine Transdermal System 7-, 14-, 21mg OTC Nicotine gum 2-, 4 mg **Other FDA-approved Products** Bupropion SR 150 mg	**Covered in the Program (not BCF)** Nicotine Nasal Spray (Nicotrol NS) Nicotine Inhalation (Nicotrol) OTC Nicotine Lozenge Varenicline (Chantix)	None	Pending publication of Final Rule Rule	Quantity limits apply to Nicotine gum and lozenge – 300 pieces/60 days	•OTC nicotine replacement products can be covered and included on the BCF, but require a prescription •2 quit attempts/120 days allowed; 3rd quit attempt requires PA
May 2012	**Newer Sedative Hypnotics (SED-1s)**	UF Class Review	Zolpidem IR Zaleplon	Zolpidem ER Eszopiclone (Lunesta) Doxepin (Silenor)	Rozerem (Ramelteon) Zolpidem sublingual (Edluar)	Pending signing of the minutes/ 60 days	Step therapy (Automated PA); requires trial of zolpidem IR or zaleplon before any other SED-1	Zolpimist not covered

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2012	**Depression and Non-opioid Pain Syndrome Agents/ GABA analog subclass**	New Drugs in Already Reviewed Class	*SSRIs:* citalopram fluoxetine sertraline *SNRIs:* venlafaxine IR venlafaxine ER *SPARIs:* trazodone *NDRIs:* bupropion HCl IR bupropion HCl SR bupropion HCl ER *GABA analogs:* gabapentin *TCAs:* amitriptyline doxepin imipramine HCl nortriptyline	*SSRIs:* fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate *SNRIs:* venlafaxine ER tablets *SARIs:* nefazodone *TCAs:* desipramine imipramine pamoate protriptyline *A2RAs:* mirtazapine tablets mirtazapine ODT	*SSRIs:* escitalopram (Lexapro) fluoxetine (Sarafem) fluoxetine weekly (Prozac Weekly) *SNRIs:* desvenlafaxine (Pristiq) duloxetine (Cymbalta) milnacipran (Savella) *SARIs:* trazodone ER (Oleptro) vilazodone (Viibryd) *NDRIs:* bupropion HBr (Aplenzin) *GABA analogs:* pregabalin (Lyrica) **gabapentin enacarbil (Horizant)** **gabapentin ER (Gralise)**	Pending signing of the minutes/ 60 days	Step therapy (Automated PA)	For step therapy: Horizant and Gralise are NF and non-step-preferred. All new users of are required to try gabapentin first.

* TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix C—Table of Abbreviations

AEs	adverse events
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
C.F.R.	Code of Federal Regulations
CMA	cost minimization analysis
CR	controlled release
CV	cardiovascular
DoD	Department of Defense
ER	extended release
FDA	U.S. Food and Drug Administration
FR	Federal Register
IR	immediate release
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
NF	nonformulary
NRT	nicotine replacement therapy
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
RAAs	Renin Angiotensin Antihypertensive Drug Class
RLS	restless leg syndrome
SED-1s	Newer Sedative Hypnotic Drug Class
SL	sublingual
UF	Uniform Formulary
U.S.C.	United States Code
VA	U.S. Department of Veterans Affairs

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
February 2012

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 16 and 17, 2012, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of November Minutes**—Jonathon Woodson M.D., Director, approved the minutes for the November 2011 DoD P&T Committee meeting on February 7, 2012.
2. **Correction of August 2011 Minutes—BCF Clarification for Non-steroidal Anti-inflammatory Drugs:** The August 2011 P&T Committee minutes were clarified to state the BCF listing is naproxen 125 mg/5 mL suspension—not ibuprofen suspension—for the oral non-steroidal anti-inflammatory drugs.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Ophthalmic-1 Class—Alcaftadine Ophthalmic Solution 0.25% (Lastacaft)

Relative Clinical Effectiveness—Alcaftadine (Lastacaft) is a dual action ophthalmic antihistamine/mast cell stabilizer. It is dosed once daily to prevent symptoms associated with allergic conjunctivitis (AC). The Ophthalmic-1 Class was evaluated for Uniform Formulary (UF) placement in February 2010. The current Basic Core Formulary (BCF) product is olopatadine 0.1% (Patanol); there are no nonformulary (NF) Ophthalmic-1 drugs.

There are no head-to-head trials with alcaftadine and the other dual action ophthalmic antihistamines. Alcafatidine was superior to placebo in preventing ocular itching

associated with AC, but was not superior in relieving conjunctival redness. Alcaftadine's safety profile appears similar to the other ophthalmic antihistamines.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) there is no evidence to suggest alcaftadine ophthalmic solution has a compelling clinical advantage over the other dual action agents for AC on the UF.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—Cost minimization analysis (CMA) was performed. The weighted average cost per day at all three points of service (POS) was evaluated for alcaftadine ophthalmic solution in relation to other currently available Ophthalmic-1 agents. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that alcaftadine ophthalmic solution was cost-effective when compared to other agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1abstained, 2 absent) alcaftadine ophthalmic 0.25% solution (Lastacaft) remain designated with formulary status on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Narcotic Analgesics—Tapentadol Extended Release Tablets (Nucynta ER)

Tapentadol extended release (Nucynta ER) is an opioid analgesic with dual modes of action; it is a mu receptor agonist with norepinephrine reuptake inhibition properties. Tapentadol ER is a Schedule II narcotic, and is classified as a high potency analgesic in the Narcotic Analgesics Drug Class. The class was last reviewed for UF placement in February 2007. Tapentadol immediate release (IR) (Nucynta) was reviewed in November 2009 and is currently NF. Tapentadol ER is indicated for moderate to severe pain when continuous, around-the-clock opioid analgesia is needed chronically. In two trials, tapentadol ER demonstrated greater reductions in pain scores compared to placebo, and produced similar reductions in pain scores as oxycodone ER (Oxycontin).

The safety profile of tapentadol ER is typical of the other high potency long-acting opioids. The adrenergic properties of the drug create additional safety concerns with respect to serotonin syndrome and interactions with monoamine oxidase inhibitors. When indirectly compared to oxycodone ER in clinical trials, the frequency of gastrointestinal (GI) adverse events (constipation, nausea, and vomiting) was observed less frequently in the Nucynta ER treatment groups. However, there were more central nervous system (CNS) disorders seen in the Nucynta ER groups.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that tapentadol extended release (Nucynta ER) offers another long-acting, high-potency narcotic analgesic treatment option that may have less GI adverse events but more CNS adverse events than oxycodone ER. There is no evidence that pain control with tapentadol ER is superior to oxycodone ER.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—CMA was performed. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that tapentadol ER (Nucynta ER) was more costly on an average weighted cost per day of therapy basis than several other comparators in the high potency narcotic analgesics currently on the UF, including generic morphine sulfate IR and fentanyl patches. Tapentadol ER was less costly than morphine sulfate ER (Avinza and Kadian), oxymorphone ER (Opana ER), oxycodone ER (OxyContin), and hydromorphone ER (Exalgo).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (9 for, 8 opposed, 1abstained, 0 absent) tapentadol extended release (Nucynta ER) remain formulary on the UF. UF status was designated due to the potential for decreased GI intolerance as compared to oxycodone ER, despite the concerns of potential undesirable drug interactions due to norepinephrine reuptake inhibition properties.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Antiplatelet Agents

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the antiplatelet drugs, which are used for treating acute coronary syndromes, stroke, and peripheral artery disease. The Antiplatelet Drug Class is comprised of the following: clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ticlopidine (Ticlid, generics), aspirin/dipyridamole ER (Aggrenox), dipyridamole (Persantine, generics), cilostazol (Pletal, generics), and pentoxifylline (Trental, generics). Aspirin is available over-the-counter and is not part of the TRICARE® benefit.

Clopidogrel was designated with BCF status on the UF in 2002, prior to implementation of the UF Rule. Generic formulations of clopidogrel are expected in May 2012. Military Health System (MHS) expenditures for antiplatelet agents exceed $260 million annually.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusions:

1. With regard to efficacy, the following conclusions were made:
    - Acute coronary syndrome (ACS):
        - Several large clinical trials have shown the effectiveness of clopidogrel in decreasing the incidence of major cardiovascular (CV) events in patients with ACS.
        - Prasugrel and ticagrelor have a faster onset of action and exhibit more complete platelet inhibition, compared to clopidogrel.
        - Guidelines from professional cardiology groups recommend clopidogrel, prasugrel, or ticagrelor as first-line options for treating ACS patients requiring percutaneous coronary intervention (PCI).
        - Prasugrel and ticagrelor are approved solely for ACS; however, prasugrel is limited to patients whose coronary anatomy is known and suitable for PCI.
        - In the TRITON-TIMI 38 trial, prasugrel was more effective than clopidogrel in reducing the composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI), and stroke in ACS patients undergoing PCI. There was no significant difference between prasugrel and clopidogrel for the single endpoint of CV death.

- In the TRITON-TIMI 38 trial, a subgroup analysis showed prasugrel was superior to clopidogrel in patients who are diabetic, those with prior stent thrombosis, and those younger than 65 years.
- In the PLATO trial, ticagrelor was more effective than clopidogrel in reducing the composite endpoint of CV death, non-fatal MI, and stroke in ACS. Ticagrelor was more effective than clopidogrel in reducing the single endpoints of CV death and non-fatal MI, although the trial was not designed to assess differences in mortality.
- In the PLATO trial, a subgroup analysis of the 1,413 U.S. patients found no significant difference between ticagrelor and clopidogrel for major coronary events. This was attributed to the higher aspirin dose utilized in North America versus the rest of the world. Ticagrelor should only be used with aspirin doses lower than 100 mg.
- Definitive statements about comparative clinical effectiveness between prasugrel and ticagrelor are difficult to make because there are no head-to-head studies.

- Stroke
  - A systematic review from the Oregon Drug Effectiveness Review Project (DERP) concluded there was no significant difference between aspirin/dipyridamole ER and clopidogrel for all-cause mortality, CV mortality, and recurrent stroke, in patients with ischemic stroke, based on the PROFESS trial.
  - The DERP review concluded there was no significant difference between ticlopidine and clopidogrel on outcomes of all-cause mortality, CV death, or cerebral infarction in stroke patients.
- Peripheral artery disease (PAD)
  - Cilostazol is the recommended first-line agent to improve walking distance in patients with PAD, while pentoxifylline is the second-line alternative, based on professional guidelines.
  - Clopidogrel and aspirin are recommended to reduce the risk of MI, stroke or vascular death in patients with symptomatic PAD.

2. With regards to safety/tolerability, the following conclusions were made:
   - In the TRITON-TIMI 38 trial, prasugrel had a significantly higher rate of bleeding, including non-coronary artery bypass grafting (CABG) related bleeding and fatal bleeding, compared to clopidogrel.

Additional risk factors that increase the bleeding risk with prasugrel include low weight (<60 kg), age greater than 75 years, and prior history of stroke and transient ischemic attack (TIA).

- In the PLATO trial, ticagrelor had a similar rate of major and fatal bleeding compared to clopidogrel; however, the rate of non-CABG-related major bleeding was significantly higher with ticagrelor than clopidogrel. Ticagrelor was associated with a higher rate of non-hemorrhagic adverse events (AEs), including dyspnea, and increases in serum creatinine and uric acid levels.
- Unlike clopidogrel and ticagrelor, prasugrel is contraindicated in patients with previous stroke or TIA.
- Ticlopidine's therapeutic use is greatly limited by its AE profile, including risk of neutropenia and aplastic anemia.
- In stroke patients, clopidogrel had a lower rate of major bleeding and withdrawal due to AEs, compared with aspirin/dipyridamole ER.

3. With regards to other factors
   - Prasugrel and ticagrelor are less susceptible to genetic variation and drug-drug interactions with proton pump inhibitors (PPIs), compared to clopidogrel.
   - The Pharmacy Outcomes Research Team (PORT) conducted an analysis to define a typical MHS Aggrenox user. A total of 13,341 users with an average age of 76 years were identified. Over 82% of patients had received Aggrenox in the last 180 days, with a new user rate of 13%–18%, suggesting that patients had been on Aggrenox for extended periods.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the antiplatelet agents for secondary prevention in ACS, for secondary prevention in stroke, and for PAD. CMAs were performed for the antiplatelet drugs used for stroke and PAD (aspirin/dipyridamole ER, ticlopidine, cilostazol, dipyridamole, and pentoxifylline). Cost-effectiveness analyses (CEAs) and CMAs were used to analyze antiplatelet agents for ACS (clopidogrel, prasugrel, and ticagrelor), as efficacy differences between the agents were noted in the clinical review.

- CMA and BIA were used to assess the potential impact of cost scenarios where selected antiplatelet agents were designated with formulary or NF status on the UF. The impact of generic clopidogrel availability was modeled in the BIA scenarios.

- For the antiplatelet drugs prescribed following ACS, CEAs and CMAs were used to assess the potential impact of the occurrence rates of CV and bleeding events, based on differences highlighted in the clinical review.
- Two separate cost-effectiveness models were constructed in the analyses of antiplatelet agents for ACS secondary prevention: prasugrel (Effient) versus clopidogrel and ticagrelor (Brilinta) versus clopidogrel. Analysis was based on direct comparisons of relevant trial data. The models compared the annual cost per CV event avoided (the composite of nonfatal MI, nonfatal stroke, and death from CV cause).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 against, 0 abstained, 2 absent) the following:

- **Antiplatelet agents for ACS**—CEA results showed that prasugrel (Effient) and ticagrelor (Brilinta) provide reasonable clinical benefit for the increase in treatment cost, as shown by their incremental cost-effectiveness ratios (ICERs) of $28,083 and $58,358 per cardiovascular event avoided, respectively.

- **Antiplatelet agents for stroke**—CMA results showed that aspirin/dipyridamole ER (Aggrenox) was the least cost-effective agent, based on analysis of the average weighted price per day of therapy at all three POS.

- **Antiplatelet agents for PAD**—CMA results showed that pentoxifylline and cilostazol are similarly cost-effective therapy options.

- **All antiplatelet agents**—BIA results showed the scenario where all current BCF agents were retained on the BCF, all current UF agents were retained on the UF, and aspirin/dipyridamole ER (Aggrenox) and ticagrelor (Brilinta) were designated NF resulted in the lowest projected cost compared to current MHS expenditures.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 3 opposed, 0 abstained, 1 absent) clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ticlopidine (Ticlid, generics), aspirin/dipyridamole ER (Aggrenox), dipyridamole (Persantine, generics), cilostazol (Pletal, generics) and pentoxifylline (Trental, generics) remain formulary on the UF. Although the cost-effectiveness review showed aspirin/dipyridamole ER was the least cost-

effective drug for stroke, the P&T Committee recommended that it remain formulary on the UF due to the low new user rate and the advanced age of the patient population. Ticagrelor was also recommended to remain formulary on the UF due its ICER, compared to clopidogrel.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

☐ Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 0 abstained, 1 absent) clopidogrel (Plavix) maintain BCF status on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

☐ Approved, but modified as follows:

B. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The P&T Committee evaluated the relative clinical effectiveness of the DPP-4 inhibitors, which include:

- sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/simvastatin (Juvisync);
- saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR);
- linagliptin (Tradjenta).

Two new products, sitagliptin/metformin ER (Janumet XR) and linagliptin/metformin (Jentadueto) will be reviewed at an upcoming meeting. The DPP-4 inhibitors were previously reviewed in November 2010 as a subclass of the Non-insulin Diabetes Drug Class. Prior Authorization (PA) criteria and step therapy require a trial of metformin or sulfonylurea (SU) prior to using a DPP-4 inhibitor.

MHS expenditures exceed $119 million annually for DPP-4 inhibitors. In terms of overall utilization at all POS, sitagliptin and sitagliptin/metformin are the most utilized agents and are currently designated with BCF status on the UF.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the DPP-4 inhibitors:

1. Clinical practice guidelines, including the DoD/Veterans Affairs guidelines for diabetes mellitus, do not currently recommend DPP-4 inhibitors for a specific place in therapy but list the class as alternative agents. Metformin remains the recommended first line agent for most patients who do not have a contraindication for metformin therapy.
2. There are no completed long-term studies assessing CV outcomes with sitagliptin, saxagliptin, and linagliptin, although three studies are under way, with results expected in 2014–2018.
3. One head-to-head trial did not show clinically relevant differences in efficacy or safety between sitagliptin and saxagliptin.
4. Sitagliptin, saxagliptin, and linagliptin show similar effects of lowering hemoglobin A1c when used as monotherapy, ranging from 0.4% to 0.9%. When a DPP-4 inhibitor is combined with metformin, the mean decrease in A1c from baseline ranges from 0.4% to 2.5%; when combined with a thiazolidinedione (TZD), the mean decrease in A1c ranges from 0.7% to 1.06%; and when combined with a SU, the mean decrease in A1c ranges from 0.5% to 0.6%.
5. DPP-4 inhibitors are weight neutral, lipid neutral, and have minimal impact on blood pressure.
6. Linagliptin has not been directly compared with saxagliption or sitagliptin in a clinical trial. A meta-analysis showed the A1c-lowering effect of linagliptin plus metformin was non-inferior to sitagliptin plus metformin. Linagliptin is the only DPP-4 inhibitor that does not require dose adjustments due to renal or hepatic impairment.
7. Juvisync is a fixed-dose combination product containing sitagliptin with the cholesterol-lowering drug simvastatin. There are no clinical trials evaluating Juvisync; it obtained FDA approval based on bioequivalence with the individual components. Juvisync may provide a dosing convenience in patients who require both sitagliptin and a statin.
8. In terms of commonly reported adverse events, there are no clinically relevant differences between sitagliptin, saxagliptin, and linagliptin. Drug interaction profiles are also similar between agents. Pancreatitis has been reported with both sitagliptin and saxagliptin. Acute renal failure has been reported with sitagliptin.

9. There is a high degree of therapeutic interchangeability between sitagliptin, saxagliptin, and linagliptin.
10. The PORT conducted an analysis of the changes in DPP-4 inhibitor utilization following the November 2010 P&T Committee Meeting. At that meeting, sitagliptin and sitagliptin/metformin were designated BCF and step therapy (automated PA) was implemented, requiring a trial of metformin or a SU prior to use of a DPP-4 inhibitor. An increase in DPP-4 utilization has been noted at the MTF and Mail Order POS. Utilization increase at the Mail Order POS may also be due to the change in co-pay structure implemented in October 2011. There has also been a concurrent decline in TZD utilization, which is likely due to safety concerns.
11. The PORT also examined the effects of step therapy at the three POS.
    - **MTFs**—Out of 48,097 patients receiving their first DPP-4 prescription in the period from December 2010 to November 2011, 32% were new users of DPP-4 inhibitors; of these new users, 19%–21% had no evidence of prior use of metformin or SU.
    - **Retail and Mail Order**—In the 8-month evaluation period, 848 DPP-4 inhibitor prescriptions were rejected due to no evidence of prior metformin or SU use. However, 67% of these rejected prescriptions did show that a DPP-4 inhibitor prescription was received within 240 days of the reject, and 52% showed a later prescription for metformin of SU. There was no evidence of a prescription fill for any oral non-insulin diabetes drug in 12% of the rejected claims ("no fill" rate).

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—CMAs and budget impact analyses (BIA) were used to evaluate the relative cost-effectiveness of the DPP-4 inhibitors. Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- BIA was used to assess the potential impact of cost scenarios where selected DPP-4 inhibitors were designated with formulary, BCF, or NF status on the UF. The analysis included an evaluation of the potential impact of cost scenarios where DPP-4 inhibitors were designated with preferred product status (step therapy) on the UF; i.e., a trial of a preferred DPP-4 inhibitor would be required before using other DPP-4 inhibitors on the UF.
- BIA results showed the scenario where sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/simvastatin (Juvisync) are step-preferred on the UF, linagliptin (Tradjenta) is non-preferred on the UF, and saxagliptin

(Onglyza) and saxagliptin/metformin (Kombiglyze XR) are non-preferred and NF was determined to be the most cost-effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 1 opposed, 1 abstained, 0 absent):

   - sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/simvastatin (Juvisync) be designated step-preferred and formulary on the UF;
   - linagliptin (Tradjenta) be designated non-preferred and formulary on the UF;
   - saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR) be designated non-preferred and NF.

   This recommendation implements step therapy, which requires a trial of Januvia, Janumet, or Juvisync (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors would require a trial of metformin or sulfonylurea for new patients.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***— Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) sitagliptin (Januvia) and sitagliptin/metformin (Janumet) maintain BCF status on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluations for saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR) and the conditions for establishing MN for NF medications, the P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR). (See Appendix C for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

      (2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual PA criteria for Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta, if automated criteria are not met:

      (1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.

(2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

(3) The patient has a contraindication to both metformin and a SU.

c) In addition to the above criteria regarding metformin and SU, the following PA criteria would apply specifically to saxagliptin (Onglyza), saxagliptin/ metformin ER (Kombiglyze XR), and linagliptin (Tradjenta):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with saxagliptin- or linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***— The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is July 11, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Attention Deficit Hyperactivity Disorder (ADHD)/Wakefulness-Promoting Agents

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the ADHD and Wakefulness-Promoting Agents Class, which was previously reviewed in November 2006. The drugs in this class are comprised of the following three subclasses: 1) ADHD stimulants, 2) ADHD non-stimulants, and 3) wakefulness-promoting agents.

The ADHD stimulants include lisdexamphetamine (Vyvanse), and long- and short-acting formulations of methylphenidate, amphetamine, and mixed amphetamine salt products. The full list of the drugs in the subclass and the classification of long- and short-acting stimulants are found in Appendix D. Since the November 2006 review, dexmethylphenidate IR (Focalin), mixed amphetamine salts ER and IR (Adderall XR; Adderall), and methylphenidate long-acting (LA) (Ritalin LA) are now available in generic formulations. There is one authorized generic for methylphenidate osmotic-controlled release oral delivery system (OROS), which is produced by the manufacturer of Concerta.

The ADHD non-stimulants subclass is comprised of atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv). The wakefulness-promoting subclass includes modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). Generic formulations of modafinil are expected in the 2nd quarter of 2012. Prior Authorization is currently required for modafinil and armodafinil.

The current BCF agents include mixed amphetamine salts ER (Adderall XR, generics), methylphenidate IR (Ritalin, generic) and methylphenidate OROS (Concerta). The current NF products include dexmethylphenidate ER (Focalin XR), dexmethylphenidate IR (Focalin), lisdexamfetamine (Vyvanse), and methylphenidate transdermal system (Daytrana).

Relative Clinical Effectiveness Conclusion

1. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the ADHD stimulants and non-stimulants:
    a) Methylphenidate IR is more effective than placebo in improving ADHD symptoms in preschool-aged children (4–5 years of age) who do not respond to parental behavior training.
    b) Based on a DERP systematic review, the following conclusions apply in children and adolescents aged 6–17 years:
        - There are no clinically relevant differences between the IR stimulant formulations.
        - There are no clinically relevant differences between IR stimulant formulations when compared to sustained release (SR) stimulants (Ritalin SR, Metadate CD).
        - There is conflicting evidence when methylphenidate IR is compared with methylphenidate OROS (Concerta). Two double-blinded studies showed no difference in efficacy, while two open-label studies favored methylphenidate OROS.

- There are no clinically relevant differences when SR stimulant formulations are compared to other SR formulations. Minor differences include that methylphenidate CD (Metadate CD) and dexmethylphenidate ER (Focalin XR) show greater response in the morning, while methylphenidate OROS (Concerta) shows greater response in the evening.
- Lisdexamphetamine (Vyvanse) treatment resulted in similar scores on AHDH rating scales when compared to mixed amphetamine salts ER (Adderall XR).
- Transdermal methylphenidate (Daytrana) produced similar scores on investigator, teacher, and parent rating scales when compared to methylphenidate OROS (Concerta) over a 7-week period.

c) In adults (18 years of age and older), there are no clinically relevant differences in efficacy when switching to methylphenidate OROS (Concerta) versus continuing with methylphenidate IR.

d) With regards to safety, package labeling for all stimulants contains a black box warning for potential abuse and dependency.

e) Use of mixed amphetamine salts (Adderall IR, generic) is associated with a higher incidence of weight loss and insomnia than methylphenidate IR.

f) One large randomized controlled trial, the Multimodal Therapy Study of ADHD, reported stimulants caused a decrease in growth velocity in children at 36 months.

g) Stimulants do not significantly increase the risk of serious cardiovascular events in children, adolescents, or adults (up to age 64), based on two large cohort studies.

h) The stimulants with the lowest potential for abuse/diversion are Vyvanse, Daytrana, and Concerta. In adolescents, American Academy of Pediatrics guidelines recommend prescribing non-stimulants or stimulants with the lowest potential for abuse/diversion, compared to the other stimulant products.

i) For patients with swallowing difficulties, Vyvanse is dissolvable in water. Ritalin LA, Metadate CD, Adderall XR, and Focalin XR are formulated in capsules that can be opened and sprinkled on food.

j) The PORT analyzed ADHD prescription use in the MHS for the first 4 months of the school year.

(1) Use of any ADHD medication is highest among 6–12 year olds (33%) and 13–17 year olds (20%), and declines with age. Use of a

specific long-acting stimulants varies by age group, with Concerta predominating in patients younger than 18, and Adderall XR or its generic predominating in patients older than 18.

(2) Overall, 62% of usage is for a long-acting stimulant alone without another ADHD drug. About 14% of ADHD prescriptions were for a long-acting stimulant with a short-acting stimulant, which varied from 9% with Vyvanse, 11% with Concerta, and up to 27% with Ritalin LA.

2. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the ADHD non-stimulants:

a) The DERP systematic review concluded atomoxetine (Strattera) is associated with efficacy outcomes similar to methylphenidate IR. Methylphenidate OROS (Concerta) and mixed amphetamine salts ER (Adderall XR, generic) are superior to atomoxetine in terms of response rates.

b) There are no head-to-head trials comparing clonidine ER (Kapvay) or guanfacine ER (Intuniv) with other ADHD drugs. Placebo-controlled studies with clonidine ER showed modest benefit when used as add-on or monotherapy. Placebo-controlled studies with guanfacine ER (Intuniv) showed modest benefit up to 8 hours after dosing.

c) With regards to safety, the package labeling for atomoxetine (Strattera) contains a black box warning for suicidal ideation. Atomoxetine has a higher incidence of vomiting, nausea, and somnolence compared to stimulants.

d) Clonidine ER (Kapvay) and guanfacine ER (Intuniv) are associated most commonly with somnolence and fatigue, although there are no comparative data with other ADHD drugs.

3. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the wakefulness-promoting drugs:

a) A large percentage (estimated 90%) of modafinil (Provigil) and armodafinil (Nuvigil) MHS prescriptions are for non-FDA approved indications.

b) There is one head-to-head trial comparing modafinil 200 mg with armodafinil 150 mg in patients with excessive sleepiness due to shift work sleep disorder. There was no significant difference between the two drugs in terms of percentage of responders at 12 weeks.

c) There are no head-to-head trials comparing modafinil with armodafinil in patients with narcolepsy or obstructive sleep apnea.

d) The manufacturer of armodafinil (Nuvigil) submitted data to the FDA requesting approval for patients with jet lag, but the application was denied.

e) The manufacturer of sodium oxybate (Xyrem) sought FDA approval for use in fibromyalgia, but was denied due to abuse potential and safety concerns.

f) With regards to safety and tolerability, there are no clinically relevant differences in the safety profiles between modafinil and armodafinil.

g) Sodium oxybate (Xyrem) has a black box warning for abuse/misuse/diversion potential. A restricted distribution program limits dispensing to one centralized pharmacy.

h) The PORT analyzed usage of modafinil (Provigil) and armodafinil (Nuvigil) in the MHS. For the patients who received armodafinil, 32% were new users; of these new users, only 6% of patients had a previous prescription for modafinil in the previous 180 days, suggesting that the majority of new armodafinil users do not first receive a trial of modafinil.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of ADHD long-acting stimulants, short-acting stimulants, and non-stimulants, and the wakefulness-promoting agents. CMAs were performed to compare average daily cost of therapy for all branded and generic drugs within each of the respective subclasses. BIAs of varying formulary scenarios where various agents moved between BCF, UF, and NF status were performed for the long-acting stimulants, the non-stimulants, and the wakefulness-promoting drugs.

- *ADHD*—BIA was used to evaluate the long-acting stimulants, with corresponding sensitivity analyses. For relative comparison with the long-acting stimulants, a composite average daily cost for the short-acting stimulants was also calculated.

- *Wakefulness-promoting agents*—CMA and BIAs were used to evaluate the drugs in this subclass, with corresponding sensitivity analyses. BIAs also considered the potential impact of cost scenarios where current armodafinil (Nuvigil) users were grandfathered (and prior authorization would only apply to new users) versus a no-grandfathering scenario with prior authorization applicable to all users. Sodium oxybate (Xyrem) was not included in the CMA or BIAs due to restricted distribution from one pharmacy. Generic pricing estimates for

modafinil (Provigil) were used in the cost analyses based on its anticipated generic availability.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded the following for the ADHD and wakefulness-promoting agents:

1. The P&T Committee agreed (17 for, 0 opposed, 1 abstained, 0 absent) on the following conclusions regarding the long-acting stimulants: CMA results showed the following ranking, from least costly to most costly: mixed amphetamine salts ER < Ritalin LA < Vyvanse < Focalin XR < Concerta < Daytrana. BIAs results showed that scenarios where the current branded NF long-acting stimulants remained NF generated greatest cost avoidance.
2. The P&T Committee agreed (17 for, 0 opposed, 1 abstained, 0 absent) on the following conclusions regarding the short-acting stimulants: CMA results showed the following ranking, from least costly to most costly: methylphenidate IR (Ritalin generic) < dextroamphetamine tablets (Dexedrine generic) < mixed amphetamine salts (Adderall generic) < dexmethylphenidate (Focalin generic) < methylphenidate SR (Ritalin SR generic) < Metadate CD < Methylin chewable tablet < dextroamphetamine spansules (Dexedrine generic) < Procentra liquid < Desoxyn. Composite costs results showed the short-acting stimulants were more cost-effective than the long-acting stimulants.
3. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) on the following: for the non-stimulants, Strattera was most cost-effective, followed by Intuniv; Kapvay was least cost-effective. BIAs results showed minimal differences in cost-avoidance between branded NF and UF non-stimulants.
4. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) on the following: for the wakefulness-promoting agents, CMA showed the estimated generic modafinil was most cost-effective, followed by Provigil; Nuvigil was least cost-effective. BIAs results showed that scenarios where Nuvigil changes to NF status and all current and new users of Nuvigil undergo the PA process (e.g., not grandfathered) generated greatest cost-avoidance; this scenario also included maintaining the existing PA for Provigil.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

Drugs designated with formulary status on UF	For	Opposed	Abstain	Absent
Stimulants: dextroamphetamine (Dexedrine, Dextrostat, Procentra solution, generics) methamphetamine HCl (Desoxyn, generic) methylphenidate CD (Metadate CD) methylphenidate IR (Ritalin, generic) methylphenidate LA (Ritalin LA, generic) methylphenidate ER (Metadate ER, Methylin ER, generics) methylphenidate chewable tablets, solution (Methylin, generic) methylphenidate OROS (Concerta) methylphenidate SR (Ritalin SR, generic) mixed amphetamine salts IR (Adderall, generic) mixed amphetamine salts ER (Adderall XR, generic)	15	1	1	1
Non-Stimulants:* atomoxetine (Strattera) clonidine ER (Kapvay) guanfacine ER (Intuniv)	16	0	1	1
Wakefulness-Promoting Agents: modafinil (Provigil) sodium oxybate (Xyrem)	16	0	1	1

* Clonidine IR tablets and transdermal system (Catapress, Catapress patch, generic) and guanfacine IR (Tenex, generics) are designated UF in the Miscellaneous Anti-hypertensive Agents Drug Class.

Drugs designated with NF status on UF:	For	Opposed	Abstain	Absent
Stimulants: desmethylphenidate ER (Focalin XR) lisdexamphetamine (Vyvanse) methylphenidate transdermal system (Daytrana)	15	1	1	1
Non-Stimulants: None designated NF	16	0	1	1
Wakefulness-PromotingAgents: armodafinil (Nuvigil)	16	0	1	1

* Clonidine IR tablets and transdermal system (Catapress, Catapress patch, generic) and guanfacine IR (Tenex, generics) are designated UF in the Miscellaneous Anti-hypertensive Agents Drug Class.

Drugs approved to move from NF status to Formulary status on UF:	For	Opposed	Abstain	Absent
Stimulants: dexmethylphenidate IR (Focalin, generic)	15	1	1	1

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended:

Drugs designated with BCF status:	For	Opposed	Abstain	Absent
Stimulants: mixed amphetamine salts ER (Adderall XR, generic) methylphenidate IR (Ritalin, generic) methylphenidate LA (Ritalin LA, generic)† methylphenidate OROS (Concerta) *Non-stimulants*:* None designated BCF *Wakefulness-Promoting:* None designated BCF	14	2	1	1

† Ritalin LA was added to the BCF, to have the most cost-effective long-acting methylphenidate formulation available at all MTFs. Concerta was maintained on the BCF, due to the large numbers of pediatric patients currently stabilized on the drug. Ritalin LA is encouraged to be considered in new patients requiring a long-acting methylphenidate formulation.

* Clonidine IR tablets (Catapress, generic) are designated BCF in the Miscellaneous Anti-hypertenisve Agents Drug Class.

Director, TMA, Decision: ☒ ~~Approved~~ ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluations for theADHD stimulants [dexmethylphenidate ER (Focalin XR), lisdexamphetamine (Vyvnase) and methylphenidate transdermal system (Daytrana)] , the wakefulness-promoting agents [armodafinil (Nuvigil)], and the conditions for establishing MN for NF medications, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) MN criteria for armodafinil (Nuvigil) and maintaining the current MN criteria for Focalin XR, Vyvanse, and Daytrana. (See Appendix C for full MN criteria.)

Director, TMA, Decision: ☒ ~~Approved~~ ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: PA CRITERIA***— The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) PA criteria should apply to modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). The current PA criteria for modafinil were recommended to be continued without modification. The P&T Committee recommended maintaining the current PA criteria for Nuvigil, with one modification; jet lag would be added to the list of uses not provided. Additionally, the recommendation was that all current and new users of Nuvigil must undergo the PA process. The P&T Committee recommended PA criteria for sodium oxybate, which would be provided only for the current FDA-approved indications. Prior authorization is not intended to apply to modafinil or armodafinil use in active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use. (See Appendix B for full PA criteria).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD*** —The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is July 11, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. Crizotinib (Xalkori)—PA: Crizotinib (Xalkori) is an oral anaplastic lymphoma kinase (ALK) inhibitor indicated for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC) as detected by a FDA-approved diagnostic test. The FDA has approved a new molecular diagnostic test (Vysis ALK FISH Probe test) designed to

identify ALK-positive NSCLC patients for treatment with Xalkori.

1. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to Xalkori capsules, consistent with the FDA-approved product labeling:

    a) Coverage would be approved for the treatment of patients with documented diagnosis of ALK-positive NSCLC, detected by a FDA-approved test such as Vysis ALK FISH Probe test.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows: The approved PA limits coverage of the drug to its labeled use. TMA will expedite review of the required test to determine its coverage under 32 CFR 199.4(g)(15). Providers and beneficiaries will be advised to retain receipts for the test for submission for reimbursement following the coverage determination.

B. Crizotinib (Xalkori)—Quantity Limits (QLs): QLs and/or days supply limits currently apply to several oral chemotherapy agents. Xalkori is only available at the retail point of service through five specialty pharmacies (Curascript, Acredo, Walgreen's, CVS Caremark, and US Bioservices).

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) QLs/days supply limits, restricting the maximum allowable quantity to a 30-day supply at the retail point of service. This is consistent with supply limits for other oral chemotherapy agents.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Vermurafenib (Zelboraf)—PA: Vermurafenib (Zelboraf) is an oral kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation. Zelboraf is not recommended for use in wild-type BRAF melanoma. The FDA also approved a new molecular diagnostic test (Cobas 4800) designed to detect the $BRAF^{V600E}$ mutation and identify patients likely to respond to Zelboraf therapy.

1. ***COMMITTEE ACTION: PA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) the following PA criteria should apply to Zelboraf tablets, consistent with the FDA-approved product labeling.

    a) Coverage will be approved for the treatment of patients with documented diagnosis of unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation, detected by a FDA-approved test such as Cobas 4800.

    b) Coverage will not be approved for patients with wild-type BRAF melanoma.

Director, TMA, Decision: ☐ Approved ☐ Disapproved

Approved, but modified as follows: The approved PA limits coverage of the drug to its labeled use. TMA will expedite review of the required test to determine its coverage under 32 CFR 199.4(g)(15). Providers and beneficiaries will be advised to retain receipts for the test for submission for reimbursement following the coverage determination.

D. Vermurafenib (Zelboraf)—QLs: QLs and/or days supply limits currently apply to several oral chemotherapy agents.

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) QLs/days supply limits, restricting the maximum allowable quantity to a 30-day supply at the retail point of service and a 45-day supply at Mail Order. This is consistent with supply limits for other oral chemotherapy agents.

Director, TMA, Decision: ☐ Approved ☐ Disapproved

Approved, but modified as follows:

E. Ivacaftor (Kalydeco)—PA: Ivacaftor (Kalydeco) is a new oral agent that targets a specific subgroup of patients with Cystic Fibrosis (CF). It is a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR). Kalydeco is indicated for the treatment of CF in patients aged 6 years of age and older who have a G551D mutation in the CFTR gene. This rare mutation occurs in about 4% of CF patients. In patients for whom the genotype is unknown, a FDA-approved test should be used to detect the presence of the G551D mutation. Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene, which occurs in about 90% of

CF patients. There are several FDA-approved in-vitro molecular diagnostic tests designed to simultaneously detect and identify mutations in the CFTR gene.

1. ***COMMITTEE ACTION: PA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) the following PA criteria should apply to Kalydeco tablets, consistent with the FDA-approved product labeling:
   a) Coverage will be approved for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene, detected by a FDA-approved test.
   b) Coverage will not be approved for patients who are homozygous for the F508del mutation in the CFTR gene.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows: The approved PA limits coverage of the drug to its labeled use. TMA will expedite review of the required test to determine its coverage under 32 CFR 199.4(g)(15). Providers and beneficiaries will be advised to retain receipts for the test for submission for reimbursement following the coverage determination.

F. Ivacaftor (Kalydeco)—QL: Quantity limits/days supply limits were recommended for Kalydeco.

1. ***COMMITTEE ACTION: QL***—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) QLs/days supply limits, restricting the maximum allowable quantity to a 30-day supply at the retail point of service and a 45-day supply at Mail Order.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

G. *COMMITTEE ACTION: PA IMPLEMENTATION PERIOD FOR XALKORI, ZELBORAF, AND KALYDECO*—The P&T Committee recommended (16 for, 0

opposed, 1 abstain, 1 absent) an effective date of the first Wednesday after a 30-day implementation period in all points of service. The effective date is July 11, 2012.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VII. SECTION 703

A. Section 703—The P&T Committee reviewed a list of products—Alocril, Avage, Azelex, Betagan, Blephamide, Elestat, Elimite, FML, FML Forte, FML S.O.P., Ocufen, Ocuflox, Poly-Pred, Poly-Trim, Pred Mild, Pred-G, and Transderm-Scop—to determine MN and PA criteria. These products were identified as not fulfilling refund requirements as required in section 703 of the 2008 National Defense Authorization Act (NDAA). The listed medications were designated NF on the UF at previous P&T Committee meetings.

1. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following should apply to the listed drugs. Coverage at retail network pharmacies would be approved if the patient met all the following criteria:

    a) Manual PA criteria:

        (1) Use of formulary agent is contraindicated.

        (2) Obtaining the product from home delivery would be detrimental to the patient.

        (3) For branded products with AB generic availability, use of the generic product would be detrimental to the patient.

The PA criteria listed above do not apply to any point of service other than retail network pharmacies.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following should apply to the listed drugs:

    a) Use of formulary agent is contraindicated.

Director, TMA, Decision: □ ~~Approved~~ □ Disapproved

Approved, but modified as follows:

VIII. ITEMS FOR INFORMATION

A. The PORT provided the P&T Committee with an update and review of findings on various topics:

- *Comparative costs across pharmacy POS*—Based on an analysis of all non-specialty maintenance medications filled at all three pharmacy POS, the mean cost for a 90-day supply appears to be about 19% lower at MTFs or mail order compared to retail for 4QFY11, adjusting for FY12 co-pay changes. The difference was driven by brand-only medications, which were about 27% lower at MTFs or mail compared to retail; generically available medications were either similar across POS or slightly higher at MTFs/mail order compared to mail order (+2%). This represents a narrowing of the gap between POS; a similar analysis for 4QFY10 showed costs at MTFs/mail order to be about 25% lower overall versus retail, with brand-only and generic medications running about 30% and 15% lower, respectively. Cost differences between MTFs and mail order remained minimal.

- Effective October 1, 2011, co-pays changed from $3 to $0 for Tier 1 medications at mail order; $3 to $5 for Tier 1 medications at retail; $9 to $12 for Tier 2 medications at retail [remaining at $9 in mail order]; and $22 to $25 for Tier 3 medications at both mail order and retail. The PORT reported an increase in mail order utilization during the first four months following the change, most prominently for generic but also occurring for branded medications. The trend continued across all POS towards increased generic use, consistent with recent generic availability for several widely-used medications.

- The PORT also provided a list of the top 100 outpatient medications by DoD expenditures for 1QFY12, which represent about 64% of costs across all POS. Of these, 76 are in classes already reviewed by the P&T Committee at least once. The data facilitated a discussion of potential future drug class reviews.

- The PORT also reported preliminary results from a study of the effect of co-pay differences on medication adherence among DoD beneficiaries, performed in conjunction with the MHS Scientific Advisory Panel. Final results are expected shortly.

IX. CLASS OVERVIEWS

Two drug class overviews were presented to the P&T Committee. The Newer Insomnia Agents Drug Class was last reviewed in February 2007. The Smoking Cessation Drug Class has not previously been reviewed by the P&T Committee. The DoD is currently reviewing a proposed rule to establish a TRICARE smoking cessation program; see Section 713 of the Duncan Hunter NDAA for Fiscal Year 2009. The P&T Committee is responsible for identifying and evaluating pharmaceutical products available through this program, consistent with 32 CFR 199.21(e)(1). The clinical and economic analyses of these classes will be presented at an upcoming meeting.

X. ADJOURNMENT

The meeting adjourned at 1100 hours on February 17, 2012. The next meeting will be in May 2012.

Appendix A—Attendance: February 2012 P&T Committee Meeting

Appendix B—Prior Authorization Criteria for the Wakefulness-Promoting Drug Class

Appendix C— Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Appendix E—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

7 May 2012
(Date)

Appendix A—Attendance: February 2012 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Deborah Thompson	Coast Guard, Pharmacy Officer
CDR Traci Hindman, MSC for CAPT Edward Norton, MSC	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT David Tanen, MC	Navy, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Bruce Lovins, MC	Army, Family Practice Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
Dr. Miguel Montalvo	TRICARE® Regional Office-South Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
CDR Jay Peloquin	Defense Logistics Agency Troop Support
Guests	
Capt Nita Sood via DCO	Pharmacy Operations Directorate
LCDR Charles McKee	Indian Health Service

Appendix A—Attendance: February 2012 P&T Committee Meeting (continued)

Guests	
LCDR David Sohl	University of Texas Masters Student
Ms Melanie Richardson via DCO	Pharmacy Operations Directorate
Others Present	
Lt Col Rey Morales, MC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
MAJ Misty Cowan, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Maj David Folmar, BSC	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Bradley Clarkson	Pharmacy Resident
Capt Danial Oh via DCO	San Antonio Major Medical Command Pharmacy Resident

Appendix B—Prior Authorization Criteria for the Wakefulness-Promoting Drug Class

	Modafinil (Provigil)	Armodafinil (Nuvigil)	Sodium Oxybate (Xyrem)
Prior Authorization	Coverage provided for the treatment of: ▪ Excessive daytime sleepiness associated with narcolepsy, as diagnosed by polysomnogram or MSLT objective testing ▪ Excessive daytime sleepiness associated with OSAHS, only after adequate titration of CPAP treatment ▪ Excessive sleepiness associated with SWSD, only in patients who work night shifts ▪ Excessive fatigue associated with multiple sclerosis, only after secondary causes of fatigue have been addressed ▪ Excessive fatigue associated with myotonic dystrophy ▪ Depression, only after primary therapy has failed and if the use of other stimulant augmentation is contraindicated ▪ Idiopathic hypersomnia diagnosed by a sleep specialist ▪ Fatigue associated with traumatic brain injury Coverage NOT provided for the treatment of other conditions not listed above, including the following: ▪ Chronic fatigue syndrome ▪ Stroke rehabilitation ▪ Appetite suppression ▪ Parkinson's disease	Coverage provided for the treatment of: ▪ Excessive daytime sleepiness associated with narcolepsy, as diagnosed by polysomnogram or MSLT objective testing ▪ Excessive daytime sleepiness associated with OSAHS, only after adequate titration of CPAP treatment ▪ Excessive sleepiness associated with SWSD, only in patients who work night shifts Coverage NOT provided for the treatment of other conditions not listed above, including the following: ▪ Jet lag ▪ Excessive fatigue associated with multiple sclerosis ▪ Excessive fatigue associated with myotonic dystrophy ▪ Depression ▪ Idiopathic hypersomnia ▪ Fatigue associated with traumatic brain injury ▪ Chronic fatigue syndrome ▪ Stroke rehabilitation ▪ Appetite suppression ▪ Parkinson's disease	Coverage provided for the treatment of: ▪ Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy, diagnosed by polysomnogram and MSLT ▪ Excessive sleepiness associated with narcolepsy without cataplexy, if the patient has previously tried modafinil (Provigil) Coverage NOT provided for the treatment of other conditions not listed above or any non-FDA approved use, including the following: ▪ Fibromyalgia ▪ Insomnia ▪ Excessive sleepiness not associated with narcolapsy

CPAP: continuous positive airway pressure
MSLT: mean sleep latency time
OSAHS: obstructive sleep apnea/hypopnea syndrome
SWSD: shift work sleep disorder

Appendix C—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Saxagliptin (Onglyza) Saxagliptin/Metformin ER (Kombiglyze XR) **Non-insulin Diabetes Drugs: DPP-4 Inhibitors**	• Use of formulary DPP-4 agents contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary DPP-4 inhibitors
Dexmethylphenidate ER (Focalin XR) Lisdexamphetamine (Vyvanse) Methylphenidate transdermal (Daytrana) **ADHD/Wakefulness-Promoting Drugs: Stimulants Subclass**	No change from previous MN criteria • Use of formulary ADHD stimulants is contraindicated • The patient has experienced significant adverse effects from formulary ADHD stimulants • Use of the formulary stimulants has resulted in therapeutic failure • For Daytrana: No alternative formulary agent available—the patient is unable to take oral medications
Armodafinil (Nuvigil) **ADHD/Wakefulness-Promoting Drugs: Wakefulness-Promoting Subclass**	• Use of modafinil (Provigil) is contraindicated

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2012	**Antiplatelet Agents**	UF Class Review	▪ Clopidogrel (Plavix)	▪ Prasugrel (Effient) ▪ Ticagrelor (Brilinta) ▪ Aspirin/dipyridamole ER (Aggrenox) ▪ Ticlopidine (Ticlid, generics) ▪ Cilostazol (Pletal), generics) ▪ Dipyridamole (Persantine, generics) ▪ Pentoxifylline (Trental, generics)	▪ - Not applicable (no drug designated nonformulary)	Pending signing of minutes/ 60 days	Not applicable	▪ Clopidogrel remains BCF
Feb 2012	**Non-Insulin Diabetes Drugs** **DPP-4 Inhibitors**	UF Class Review	▪ Sitagliptin (Januvia) ▪ Sitagliptin/Metformin (Janumet)	▪ Sitagliptin/Simvastatin (Juvisync) ▪ Linagliptin (Tradjenta)	▪ Saxagliptin (Onglyza) ▪ Saxagliptin/Metformin ER (Kombiglyze XR)	Pending 60 days	Step therapy required – see comments	▪ Must try metformin and sulfonylurea 1st before any DPP-4 drug ▪ Must try sitagliptin-containing product 1st before Onglyza, Kombiglyze XR, and Tradjenta
Feb 2012	**ADHD / Wakefulness-Promoting Drugs** **Wakefulness-Promoting Drugs**	UF Class Review	▪ Not applicable	▪ Modafinil (Provigil) ▪ Sodium oxybate (Xyrem) – restricted distribution	▪ Armodafinil (Nuvigil)	Pending 60 days	PA required – see comments	▪ All current and new users of Nuvigil must go through PA process

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2012	**ADHD / Wakefulness-Promoting Drugs** **ADHD Stimulants**	UF Class Review	**Long-acting stimulants** ▪ Mixed amphetamine salts ER (Adderall XR generics) ▪ Methylphenidate LA (Ritalin LA, generic) ▪ Methylphenidate OROS (Concerta **Short-acting stimulants** ▪ Methylphenidate IR (Ritalin, generic)	**Short-acting stimulants** ▪ Mixed amphetamine salts IR (Adderall, generic) ▪ Dexmethylphenidate IR (Focalin, generic) ▪ Dextroamphetamine (Dexedrine, Dextrostat, Procentra solution) ▪ Methylphenidate CD (Metadate CD) ▪ Methylphenidate ER (Metadate ER, Methylin ER, generic) ▪ Methylphenidate chewable tablets, solution (Methylin, generic) ▪ Methylphenidate SR (Ritalin SR, generic) ▪ Methamphetamine HCl (Desoxyn)	**Long-acting stimulants** ▪ Dexmethylphenidate ER (Focalin XR) ▪ Lisdexamphetamine (Vyvanse) ▪ Methylphenidate transdermal system (Daytrana)	Pending 60 days	Not applicable	▪ Ritalin LA now BCF
Feb 2012	**ADHD / Wakefulness-Promoting Drugs** **ADHD Non-Stimulants**	UF Class Review	▪ Not applicable	▪ Atomoxetine (Strattera) ▪ Clonidine ER (Kapvay) ▪ Guanfacine ER (Intuniv)	▪ Not applicable (no nonformulary drugs)	Pending 60 days	Not applicable	▪ Clonidine IR tabs are BCF ▪ Clonidine Patches and guanfacine IR (Tenex, generic are UF) in Misc Anti-hypertensive Drug Class

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2012	**Ophthalmic-1**	New Drug Review	Antihistamine/Mast Cell Stabilizers ▪ Olopatadine 0.1% (Patanol) (Aug 2010)	▪ **Alcafatinde 0.25% (Lastacaft) (Feb 2012)** August 2010 Dual Action Antihistamine/ Mast Cell Stabilizers ▪ Bepotastine (Bepreve) ▪ Olopatadine 0.2% (Pataday) ▪ Azelastine (Optivar, generics) ▪ Epinastine (Elestat) Antihistamines ▪ Emedastine (Emadine) Mast Cell Stabilizers ▪ Pemirolast (Alamast) ▪ Nedocromil (Alocril) ▪ Cromolyn (Crolom/Opticrom, generic) ▪ Lodoxamide (Alomide) NSAIDs ▪ Ketorolac 0.4% (Acular LS, generic) ▪ Ketorolac 0.45% (Acuvail) ▪ Ketorolac 0.5% (Acular, generic) ▪ Bromfenac (Xibrom) ▪ Bromfenac 0.9% (Bromday) ▪ Diclofenac (Voltaren, generic) ▪ Flurbiprofen (Ocufen, generics ▪ Nepafenac (Nevanac)	August 2010 ▪ Not applicable (no drug designated nonformulary)	Pending signing of minutes/ 60 days	Not applicable	▪ Ketotifen (Zaditor, generics) is available OTC

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2012	**Narcotic Analgesics** **Subclass: High potency single analgesic agents**	New Drug Review	High potency single analgesic agents ▪ Morphine sulfate 12 hours ER (MS Contin, generics) ▪ Morphine sulfate IR	▪ **Tapentadol extended release (Nucynta ER) (Feb 2012)** Previous Decisions ▪ Hydromorphone ER (Exalgo) ▪ Fentanyl buccal soluble film (Onsolis) ▪ Fentanyl transdermal system, transmucosal tablet (Fentora); & transmucosal lozenge ▪ Hydromorphone (Dilaudid) ▪ Levorphanol ▪ Meperidine ▪ Methadone ▪ Morphine products (other than BCF), Kadian and Avinza (ER products) ▪ Morphine sulfate ER / naltrexone (Embeda) ▪ Opium tincture ▪ Opium/belladonna alkaloids(suppositories) ▪ Oxycodone IR ▪ Oxycodone ER (Oxycontin) ▪ Oxymorphone (Opana) ▪ Oxymorphone ER (Opana ER)	▪ Tapentadol immediate release (Nucynta) (Nov 2009)	Pending signing of minutes/ 60 days	Not applicable	—

CD: controlled delivery
DPP-4: dipeptidyl peptidase-4
ER: extended release
LA: long-acting
SR: sustained release
OROS: osmotic-controlled release oral delivery system (OROS)

* TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix E—Table of Abbreviations

AC	allergic conjunctivitis
ACS	acute coronary syndrome
AEs	adverse events
ADHD	Attention Deficit Hyperactivity Disorder
ALK	anaplastic lymphoma kinase
BCF	Basic Core Formulary
BIA	budget impact analysis
CABG	coronary artery bypass grafting
CD	controlled delivery
CEA	cost-effectiveness analysis
CF	cystic fibrosis
CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
CMA	cost minimization analysis
CNS	central nervous system
CV	cardiovascular
DM	diabetes mellitus
DoD	Department of Defense
DERP	Oregon Drug Effectiveness Review Project
DPP-4	dipeptidyl peptidase-4
ER	extended release
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
ICERs	incremental cost-effectiveness ratios
IR	immediate release
LA	long-acting
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
NSCLC	non-small cell lung cancer
OROS	osmotic-controlled release oral delivery system
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PEC	Pharmacoeconomic Center
PPIs	proton pump inhibitors
PORT	Pharmacy Outcomes Research Team
POS	points of service
QLs	quantity limits
SR	sustained release
SU	sulfonylurea
TZD	thiazolidinedione
TIA	transient ischemic attack
UF	Uniform Formulary
VA	U.S. Department of Veterans Affairs

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
November 2011

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on November 9, 2011, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Jonathan Woodson M.D., Director, approved the minutes for the August 2011 DoD P&T Committee meeting on October 27, 2011.
2. **Correction of May 2011 Minutes—BCF Clarification for Risperidone:** The May 2011 P&T Committee minutes were clarified to state the BCF listing for risperidone is for the oral tablets, and does not include the orally disintegrating tablets (ODT). Risperidone orally disintegrating tablets are included on the Uniform Formulary (UF).

B. Follow-up to September Beneficiary Advisory Panel Meeting

1. A letter from a beneficiary regarding PDE-5 inhibitors was read publicly at the meeting and acknowledged by the P&T Committee.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1).

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Osteoporosis Drugs—Risedronate Delayed Release (Atelvia)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of a newly approved bisphosphonate, risedronate delayed release (DR) tablets (Atelvia). It is only approved for the treatment of postmenopausal osteoporosis. Risedronate is also available in an immediate release (IR) formulation, under the trade name Actonel, which has other FDA indications in addition to postmenopausal osteoporosis. Generic formulations of risedronate IR are expected in 2012. The

osteoporosis drug class, which includes the bisphosphonates, was reviewed for UF placement in June 2008.

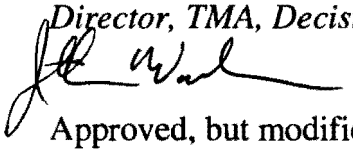
Atelvia was developed to allow coadministration with food, and it is administered immediately after breakfast. Other oral bisphosphonates (alendronate, ibandronate, risedronate IR) require administration with water 30–60 minutes in the morning prior to breakfast. Clinical trials with Atelvia have only evaluated changes in bone mineral density; there are no studies assessing Atelvia's affect on outcomes of fracture prevention.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) risedronate DR (Atelvia) offers some convenience to the patients in terms of administration schedule, but there are no studies assessing patient compliance, and it has limited clinical trial data and safety information compared to risedronate IR (Actonel). Alternative treatments are available for patients who cannot comply with the administration schedule of the other oral bisphosphonates.

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—Cost-minimization analysis (CMA) was performed. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) Atelvia was more costly when compared to other bisphosphonates on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) risedronate DR (Atelvia) be designated nonformulary (NF) .

Director, TMA, Decision: ☒Approved ☐ Disapproved



Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of risedronate DR (Atelvia) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for risedronate DR (Atelvia). (See Appendix C for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is April 18, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Depression and Non-Opioid Pain Syndrome Agents

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Depression and Non-Opioid Pain Syndrome Drug Class. The class is comprised of the former UF Antidepressants-1 (AD-1s) Drug Class [selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), serotonin antagonist reuptake inhibitors (SARIs), norepinephrine/dopamine reuptake inhibitors (NDRIs), alpha-2 receptor antagonists (A2RAs), serotonin partial agonist/reuptake inhibitors (SPARIs)]; the gamma-aminobutyric acid (GABA) analogs; and the tricyclic antidepressants (TCAs). Military Health System (MHS) expenditures for the Depression and Non-Opioid Pain Syndrome Drug Class exceed $490 million annually.

The class as a whole has not been previously reviewed; however, the AD-1s were reviewed in November 2005, and the GABA analogs were reviewed in February 2006. The drugs in this class are:

- SSRIs: citalopram, escitalopram (Lexapro), fluoxetine, fluoxetine 90 mg weekly regimen (Prozac Weekly), fluoxetine in special packaging (Sarafem), fluvoxamine, paroxetine hydrochloride (HCl) IR, paroxetine HCl controlled release (CR), paroxetine mesylate (Pexeva), sertraline

- SNRIs: duloxetine (Cymbalta), desvenlafaxine (Pristiq), milnacipran (Savella), venlafaxine IR, venlafaxine extended release (ER) capsules, venlafaxine ER tablets
- SARIs: nefazodone, trazodone IR, trazodone ER (Oleptro)
- NDRIs: bupropion HCl IR, bupropion HCl SR, bupropion ER, bupropion hydrobromide (HBr) (Aplenzin)
- A2RAs: mirtazapine tablets, mirtazapine ODT
- SPARIs: vilazodone (Viibryd)
- GABAs: gabapentin, pregabalin (Lyrica)
- TCAs: amitriptyline, desipramine, doxepin, imipramine HCl, imipramine pamoate, nortriptyline, protriptyline

The two newest entrants to the class are trazodone ER (Oleptro) and vilazodone (Viibryd). Two new gabapentin formulations have been approved by the FDA, gabapentin ER (Gralise) and gabapentin encarbil ER (Horizant), but will be reviewed at an upcoming DoD P&T Committee meeting.

For the clinical and cost effectiveness reviews, the Depression and Non-Opioid Pain Syndrome drugs were also evaluated in relation to the skeletal muscle relaxant cyclobenzaprine, and the monoamine oxidase inhibitors (MAOIs), when appropriate.

In order to support the clinical and cost-effectiveness evaluations in this complex class, the Pharmacy Outcomes Research Team (PORT) analyzed prior use of agents in this class among DoD beneficiaries initiating treatment with desvenlafaxine, duloxetine, milnacipran, or pregabalin between April 1, 2011, and June 30, 2011. A total of 135,402 new users (defined as no use of the index medication during the prior 180 days) of one of these four agents were included in the analysis.

The four study medications (desvenlafaxine, duloxetine, milnacipran, pregabalin) were chosen for analysis based on both clinical and economic considerations: all four are widely used or have potential for wide use, have alternatives that offer equal or greater clinical value, and offer the potential for minimizing costs with neutral or beneficial effects on patient outcomes. The analysis was undertaken to estimate new user rates, understand prescribing patterns, and to assess the number of beneficiaries likely to be affected by step therapy programs involving these agents.

Drugs in the class were divided into three groups (with some overlap) for purposes of the analysis:

- Group A (the four study medications): desvenlafaxine, duloxetine, milnacipran, pregabalin;
- Group B (medications used for depression): SSRIS, SNRIs (except milnacipran), TCAs, mirtazapine, bupropion, SARIs, MAOIs; and

- Group C (medications used for non-opioid pain syndromes): SNRIs including milnacipran, TCAs, cyclobenzaprine, GABA analogs (gabapentin and pregabalin).

For purposes of estimating the potential impact of step therapy programs for each of these agents, the "step-preferred" agents (medications that must be tried prior to receiving the study medication) were defined based on clinical considerations, available alternatives, and patterns of prior use.

- Desvenlafaxine is the active metabolite of venlafaxine. For the majority of patients, it offers no clinical advantage compared to the parent compound. Of 15,009 patients for whom desvenlafaxine was the index medication, only about 20% (3,057 patients) were new users; of these, 10% (299 patients) had received a previous prescription for venlafaxine. Looking back 2 years, desvenlafaxine was the first SNRI (venlafaxine, desvenlafaxine, or duloxetine) in 73% of patients, and the first medication for depression (Group B) medication in 25%. About ~11,000 new users annually could be affected by a requirement to try venlafaxine before desvenlafaxine.

- Duloxetine is an SNRI used both for depression and non-opioid pain syndromes, including fibromyalgia. Due to the complexity of depression and non-opioid pain treatment pathways and technical considerations of the step therapy look-back period, a conservative approach was taken with regard to step therapy requirements: the only patients affected are those for whom duloxetine is the first Group B or Group C medication prescribed in the last 180 days. Of 67,375 patients with duloxetine as their index medication, about 18% were new users. Of these, 64% had either a Group B or C medication. This leaves 36% of all new duloxetine users who would potentially be affected by a step therapy program that requires trial of any other Group B or C medication prior to receiving duloxetine.

- Milnacipran is an SNRI; however, in the United States it is indicated only for fibromyalgia. Accordingly, milnacipran was compared to the Group C medications, which includes other medications used for fibromyalgia. Of the 4,536 patients with milnacipran as their index medication, 26% were new users (no milnacipran in the last 180 days). Of these, 58% had a Group C medication in the last 180 days, leaving 42% of new milnacipran users who would potentially be affected by a step therapy program that requires a trial of any other Group C medication prior to receiving milnacipran.

- Pregabalin is a GABA analog similar to gabapentin, which is generically available. Both are used for neuropathic pain syndromes; there is little

clinical evidence to support a substantial difference in efficacy or safety between the two. Of 48,482 patients with pregabalin as their index medication, about 23% were new users (no pregabalin in the last 180 days). Of these, only 24% had a gabapentin Rx in the last 180 days, leaving 76% of new pregabalin users who would potentially be affected by a step therapy program that requires a trial of gabapentin prior to receiving pregabalin.

Relative Clinical Effectiveness Conclusion

1. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) upon the following conclusions regarding drugs used for depression, anxiety and other disorders (SSRIs, SNRIs, SARIs, NDRIs, A2RAs, SPARIs):
    - There are no compelling differences in efficacy to clearly differentiate one agent over the others.
    - High nonresponder rates in major depressive disorder (MDD) and anxiety disorders for each of the agents necessitate including a variety of agents on the UF.
    - Fluoxetine, and possibly escitalopram, are the only agents found to have a favorable risk to benefit profile in the treatment of MDD in children and adolescents.
    - Trials with duloxetine show no differences in efficacy with the comparator agents (fluoxetine, paroxetine, and venlafaxine), despite maximal doses of duloxetine and submaximal doses of the comparators.
    - Vilazodone is efficacious versus placebo for the treatment of MDD. Its unique mix of receptors may be beneficial to some patients. There are no head-to-head trials comparing vilazodone efficacy to other antidepressant agents and long-term data is limited.
    - Trazodone ER is efficacious versus placebo for the treatment of MDD. The effect appears to be heavily influenced by its sedating properties.
    - Mirtazapine consistently demonstrates the most rapid onset of action.
    - Beyond the FDA-indications, there is insufficient evidence to draw conclusions regarding the comparative efficacy of the antidepressants with respect to generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, or post-traumatic stress disorder.

- There is a high degree of therapeutic interchangeability for the majority of the antidepressants, when used for MDD.
- Discontinuation rates due to adverse events (AEs) are similar between agents.
- There is wide variation in the specific AE profiles of the antidepressant agents, which is due to their differences in receptor binding properties.
- Factors including activation/sedation properties, weight changes, sexual dysfunction, drug interactions (most commonly based on protein-binding, cytochrome P-450 CYP isoenzyme induction/inhibition), or therapeutic duplication may guide treatment decisions in individual patients.
- Rare serious AEs for mirtazapine, nefazodone, and trazodone typically limit these drugs to second-line status.
- Minor differences in other factors including different salt forms (HCl versus HBr), delivery mechanisms (IR versus ER), or active metabolites of the parent compound (desvenlafaxine versus venlafaxine) may reduce the number of drugs with the same active ingredient that are required for inclusion on the UF.

2. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) upon the following conclusions regarding drugs used for non-opioid pain syndromes.
    - No published, direct head-to-head studies are available that compare duloxetine, milnacipran, and pregabalin for the treatment of diabetic peripheral neuropathy (DPN), fibromyalgia (FM), or post-herpetic neuralgia (PHN). Meta-analyses and systematic reviews are the primary sources for data analysis among agents.
    - Definitive statements about comparative clinical effectiveness between duloxetine and pregabalin are difficult to make given the lack of head-to-head studies.
    - The TCAs (particularly amitriptyline) and cyclobenzaprine have substantial data supporting their use, at low doses, in several pain syndromes, and are supported as first-line therapy by many clinical practice guidelines.
    - *Fibromyalgia:*
        - A meta-analysis published in JAMA 2009 concluded the following:

        - There is strong evidence for the efficacy of antidepressants (TCAs, SNRIs, SSRIs, MAOIs) in the treatment of FM.
        - Antidepressants were shown to decrease pain, sleep disturbance, and depressed mood and improve HRQoL. The effect sizes were smaller for SNRIs, SSRIs, and MAOIs than for TCAs. There is strong evidence against a favorable effect of antidepressants on improving fatigue.
    - A systematic review from the Oregon Drug Effectiveness Review Project (DERP) showed the following:
        - Paroxetine IR was superior to the TCA amitriptyline in decreasing pain and sleep disturbance in one head-to-head study.
        - Amitriptyline was similar to duloxetine, milnacipran, and pregabalin on outcomes of relieving pain and fatigue. There was insufficient data on other outcomes (changes in patient rating scales) to compare the drugs.
        - Milnacipran was inferior to duloxetine on outcomes of pain, depressed mood, and health-related quality of life (HRQoL), and inferior to both duloxetine and pregabalin on improving sleep disturbance.
        - Duloxetine was not effective in reducing pain in male, nonwhite, and older patients.
    - In a meta-analysis by Straube and colleagues, 24% of FM patients taking pregabalin at higher doses (450mg–600mg) obtained at least 50% pain relief based on the patient global impression of change rating scale. The pregabalin dose-response relationship for efficacy in FM was not as striking as that seen in other conditions.
- *Post-Herpetic Neuralgia*: According to the PLoS Medicine systematic review (2005), there is evidence of analgesic efficacy (number needed to treat < 5.0) in PHN for TCAs, opioids, gabapentin, tramadol, and pregabalin.
- *Chronic Low Back Pain* (CLBP):
    - Duloxetine has received an indication for chronic musculoskeletal pain based on studies in CLBP and osteoarthritis of the knee. Duloxetine should not be used first line for CLBP. Acetaminophen, NSAIDs, and a trial of a

TCA should be used prior to use of duloxetine for this indication.

- In the clinical trials used to obtain FDA approval for CLBP, half of the patients treated with duloxetine achieved at least a 30% improvement in pain, which is statistically significant but not clinically significant. There is a significant placebo response (~ 40%) compared to duloxetine when used for CLBP.
- Treating 5–8 patients with duloxetine resulted in modest improvement in pain (a minimally perceptible difference) in one patient treated for 13 weeks.

- *Phantom Limb Pain*
  - Only limited information is available. Current VA/DoD guidelines recommend pregabalin, gabapentin, antidepressants (e.g., SSRIs, or TCAs).
  - Two small trials (<45 patients) reported in the DERP review showed a moderate benefit with gabapentin compared to placebo.
  - There is no published data with pregabalin and a clinical trial with duloxetine was terminated early.
- Safety and Tolerability
  - Duloxetine: An additional safety warning exists regarding use in patients with hepatic impairment. Withdrawals due to AEs occurred more often with duloxetine (15%) than placebo (8%). Duloxetine is more likely to cause nausea, somnolence, constipation, and decreased appetite versus placebo.
  - Pregabalin is similar to gabapentin in AEs, although more peripheral edema and weight gain are likely with pregabalin compared to gabapentin. Pregabalin causes more dizziness and somnolence compared to placebo.
  - For both duloxetine and pregabalin, more patients with neuropathic pain discontinue taking the active drug compared with placebo.
  - Titration and tapering is required with all of the agents.
- Other factors that differentiate the drugs: Duloxetine is dosed once daily and its patent is expected to expire December 2013; pregabalin is dosed three times daily and is a controlled medication. All agents

must be dosed based on either renal or hepatic concerns. Most pharmacy benefit managers have some form of restriction in place for duloxetine, milnacipran and pregabalin.

3. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) upon the following conclusions regarding the TCAs:
    - *Depression*
        - In the primary care setting, based on one meta-analysis (McGillivray), there was a trend in favor of TCAs over SSRIs, although the p-value was not significant in terms of the weighted mean difference in depression scores. There was no significant difference between TCAs and SSRIs in terms of improvement in the Clinical Global Impression (CGI) scale.
        - Another meta-analysis (Arroll) showed that there were no apparent differences between SSRIs and TCAs in terms of an indirect comparison of the CGI, as the relative risks versus placebo were similar (1.37 with SSRIs versus 1.26 with TCAs) and the confidence intervals overlapped.
        - Use of TCAs for depression has largely been replaced by the SSRIs and SNRIs due to safety issues.
    - *DPN*: One meta-analysis (Wong) showed TCAs were significantly more effective than placebo in terms of the odds ratio for 50% decrease in pain over 3–6 weeks.
    - *Fibromyalgia*: The JAMA meta-analysis showed TCAs have large effect sizes for reducing pain, fatigue, and sleep disturbances compared to SSRIs, SNRIs, and MAOIs. There were no significant differences when amitriptyline was compared with cyclobenzaprine and nortriptyline in the DERP review.
    - *PHN*: TCAs are significantly more effective than placebo.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the depression and non-opioid pain syndrome agents. Based on the clinical findings regarding efficacy, safety, tolerability, other factors, and clinical outcomes with these agents, CMAs were performed to compare individual agents as well as combinations of these agents primarily used in the treatment of depression, non-opioid pain syndromes, or both. Budget impact analyses (BIAs) were also performed to compare competing formulary scenarios in the evaluation of the cost-effectiveness of the various groupings of these agents. Various scenarios incorporating step therapy were also evaluated, based on clinical

considerations, available alternatives, and patterns of prior use derived from the PORT analysis outlined above.

Depression Analysis: One analysis evaluated the drugs for depression, including the SSRIs, NDRIs, and the SARIs. The cost of these agents was compared across therapeutic classes in a CMA. The A2RAs, SPARIs, and TCAs were also included in this CMA.

Depression Analysis—desvenlafaxine (Pristiq) versus venlafaxine: The SNRIs (desvenlafaxine and venlafaxine) were also modeled individually in a CMA and BIA to evaluate use of step therapy, where a trial of venlafaxine would be required for new users of desvenlafaxine.

Non-Opioid Pain Syndromes Analysis—pregabalin (Lyrica) versus gabapentin: This analysis included the GABA analogs, pregabalin, and gabapentin. The cost-effectiveness of pregabalin (Lyrica) versus gabapentin was determined in a CMA and BIA to evaluate use of step therapy, where a trial of gabapentin would be required for new users of pregabalin.

Depression and Non-Opioid Pain Syndromes Analysis—duloxetine (Cymbalta) and milnacipran (Savella): CMA and BIA were used to evaluate the cost-effectiveness of duloxetine and milnacipran. The combined depression and non-opioid pain syndromes analyses were grouped into the same categories outlined in the PORT analysis. The depression analysis group ("Group B drugs") included the SSRIs, SNRIs (except milnacipran), TCAs, mirtazapine, bupropion, SARIs, and MAOIs. The non-opioid pain syndrome analysis group ("Group C drugs") included the SNRIs (with milnacipran), TCAs, cyclobenzaprine, and GABA analogs (gabapentin and pregabalin). The final analysis compared the depression and non-opioid pain syndrome drugs together. Costs for each of the subgroups, along with the individual weighted average costs for duloxetine and milnacipran, were used in the CMAs and BIAs to evaluate various step therapy scenarios for the drugs of interest: duloxetine (Cymbalta) versus the depression and non-opioid pain syndrome drugs, and milnacipran (Savella) versus the non-opioid pain syndrome drugs.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 against, 0 abstained, 0 absent) the following for the depression and/or non-opioid pain syndrome agents:

Depression Analysis: CMA results for the depression drugs [SSRIs, SARIs, NDRIs, A2RAs, SPARIs, TCAs, and MAOIs, (not including the SNRIs)], showed the following ranking, from least costly to most costly: SARIs (predominantly generic trazodone) <TCAs < A2RAs < SSRIs (using current prices for escitalopram) < NDRIs < MAOIs < SPARIs. When looking specifically at new entrants to the class, trazodone ER (Oleptro) and vilazodone (Viibryd) were less cost-effective than other antidepressants.

The same is true of bupropion HBr (Aplenzin). Several current NF antidepressants are now available or are expected to become available in cost-effective generic formulations, including escitalopram (Lexapro), fluoxetine in special packaging (Sarafem), fluoxetine weekly (Prozac weekly), and paroxetine CR (Paxil CR).

Desvenlafaxine (Pristiq) versus venlafaxine: CMA results for desvenlafaxine and venlafaxine versus the other depression drugs showed SARIs, TCAs, A2RAs, SSRIs, and NDRIs to be less costly than the SNRIs. Among the SNRIs, venlafaxine was more cost-effective than desvenlafaxine, based on cost per day of treatment. BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed the most cost-effective scenario was venlafaxine IR/ER as step-preferred on the UF/BCF, with desvenlafaxine (Pristiq) designated NF and non-step-preferred; a trial of venlafaxine IR/ER would be required for new users of desvenlafaxine. Cost-effective generic formulations of venlafaxine ER capsules are now available.

Non-Opioid Pain Syndromes Analysis and pregabalin (Lyrica) versus gabapentin: CMA results specifically focusing on pregabalin (Lyrica) versus gabapentin for non-opioid pain syndromes showed that TCAs and cyclobenzaprine, which are predominantly generic were less costly than the GABA analogs. Among the GABA analogs, gabapentin was more cost-effective than pregabalin (Lyrica), based on the cost per day of treatment between these two agents. BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed the most cost-effective scenario was gabapentin as step-preferred on the UF/BCF, with pregabalin (Lyrica) designated NF and non-step-preferred; a trial of gabapentin would be required for new users of pregabalin.

Depression and Non-Opioid Pain Syndromes Analysis and duloxetine (Cymbalta) and milnacipran (Savella): CMA results specifically focused on duloxetine (Cymbalta) versus all depression and non-opioid pain syndrome drugs (Groups B and C drugs), and milnacipran (Savella) versus all non-opioid pain syndrome drugs (Group C drugs). CMA results showed that generic SSRIs, SNRIs, SARIs, NDRIs, A2RAs, SPARIs, TCAs, MAOIs, GABA analogs and cyclobenzaprine were less costly for the treatment of depression and non-opioid pain syndromes than duloxetine (Cymbalta) or milnacipran (Savella). Milnacipran (Savella) is less costly than duloxetine (Cymbalta), based on the cost per day of treatment; however, clinical evidence and FDA labeling supports the use of duloxetine in a wider range of indications than milnacipran.

BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed that

maintaining all depression and non-opioid pain syndrome drugs in their current BCF/UF status, maintaining duloxetine and milnacipran both as NF and non-step-preferred, was the most cost-effective scenario. Since indications for use and prior medication history beyond a 180-day lookback window cannot be determined, a trial of any other Group B or C drug was required for new users of duloxetine. Similarly, a trial of any Group C drug was required for milnacipran.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

Drugs Reviewed with Formulary Status on UF List	For	Opposed	Abstain	Absent
SSRIs: citalopram fluoxetine fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate sertraline *SNRIs:* venlafaxine IR venlafaxine ER venlafaxine ER tablets *SARIs:* nefazodone trazodone *NDRIs:* bupropion HCl IR bupropion HCl SR bupropion HCl ER *TCAs:* amitriptyline desipramine doxepin imipramine HCl imipramine pamoate nortriptyline protriptyline *A2RAs:* mirtazapine tablets mirtazapine ODT	17	0	1	0
GABA analogs: gabapentin	16	1	1	0

Drugs designated with NF status on UF	For	Opposed	Abstain	Absent
SNRIs: desvenlafaxine (Pristiq)[1] *SARIs:* trazodone ER (Oleptro) *NDRIs:* bupropion HBr (Aplenzin)	17	0	1	0
SNRIs: duloxetine (Cymbalta)[2] milnacipran (Savella)[3] *GABA analogs:* pregabalin (Lyrica)[4] *SPARIs:* vilazodone (Viibryd)	16	1	1	0

Drugs approved to move from NF status to Formulary status on UF once cost-effective generic formulations become available	For	Opposed	Abstain	Absent
escitalopram (Lexapro) fluoxetine in special packaging (Sarafem) fluoxetine weekly (Prozac weekly)	17	0	1	0

[1] Desvenlafaxine (Pristiq) is nonformulary and non-step-preferred. All new users of Pristiq are required to try venlafaxine. *See* Prior Authorization Criteria, below.

[2] Duloxetine (Cymbalta) is nonformulary and non-step-preferred. All new users of Cymbalta are required to try an antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[3] Milnacipran (Savella) is nonformulary and non-step-preferred. All new users of Savella are required to try a non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[4] Pregabalin (Lyrica) is nonformulary and non-step-preferred. All new users of Lyrica are required to try gabapentin. *See* Prior Authorization Criteria, below.

Director, TMA, Decision: ☒ Approved □ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended:

Drug Class/Drug Name	Role	Approved	Abstain	Absent
SSRIs: citalopram fluoxetine, excluding fluoxetine in special packaging (Sarafem) and fluoxetine weekly (Prozac weekly) sertraline *SNRIs:* venlafaxine IR venlafaxine ER *SPARIs:* trazodone excluding trazodone ER (Oleptro) *NDRIs:* bupropion HCl IR bupropion HCl SR bupropion HCl ER *GABA analogs:* gabapentin *TCAs:* amitriptyline doxepin imipramine HCl nortriptyline	17	0	1	0

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: DESVENLAFAXINE (PRISTIQ) PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that desvenlafaxine (Pristiq) be designated step non-preferred, requiring a trial of venlafaxine in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

   a) Automated PA criteria:

      (1) The patient has filled a prescription for any venlafaxine product at any MHS pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

      (1) The patient requires treatment with an SNRI due to failure of another formulary depression agent or has experienced adverse events from the other formulary antidepressant.

      (2) The patient has a contraindication to venlafaxine or failed therapy with venlafaxine, which is not expected to occur with desvenlafaxine (Pristiq).

      (3) The patient has experienced adverse events with venlafaxine which is not expected to occur with desvenlafaxine (Pristiq).

      (4) The patient has previously responded to desvenlafaxine (Pristiq) and changing to a formulary depression agent would incur unacceptable risk.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows: The existing MN criteria are approved as the manual (paper) PA criteria. The Pharmacoeconomic Center staff may make minor changes, NOT involving changes to the underlying criteria, to prior authorization forms, such as correcting contact information or rewording clinical questions, without further involvement of the DoD P&T Committee and the Beneficiary Advisory Panel and without further approval of the Director, TMA.

4. ***COMMITTEE ACTION: PREGABALIN (LYRICA) PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that pregabalin (Lyrica) be designated non-step-preferred, requiring a trial of gabapentin in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

   a) Automated PA criteria:

      (1) The patient has filled a prescription for gabapentin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

      (1) The patient has failed therapy with gabapentin or the formulary non-opioid pain syndrome agents.

      (2) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents which is not expected to occur with pregabalin (Lyrica).

      (3) The patient has experienced adverse events with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with pregabalin (Lyrica).

(4) The patient has previously responded to pregabalin (Lyrica).and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

Director, TMA, Decision: ☒Approved ☐ Disapproved

Approved, but modified as follows: The existing MN criteria are approved as the manual (paper) PA criteria. The Pharmacoeconomic Center staff may make minor changes, NOT involving changes to the underlying criteria, to prior authorization forms, such as correcting contact information or rewording clinical questions, without further involvement of the DoD P&T Committee and the Beneficiary Advisory Panel and without further approval of the Director, TMA.

5. ***COMMITTEE ACTION: DULOXETINE (CYMBALTA) PA CRITERIA***— The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that duloxetine (Cymbalta) be designated non-step-preferred, requiring a trial of any antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

   a) Automated PA criteria:

      (1) The patient has filled a prescription for any antidepressant (Group B) or non-opioid pain medicine (Group C) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met: PA will be developed from existing MN criteria. The existing MN criteria are as follows:

      (1) The patient has failed therapy with failed therapy with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).

(2) The patient has a contraindication to the formulary depression/non-opioid pain syndrome agents which is not expected to occur with duloxetine (Cymbalta).

(3) The patient has experienced adverse events with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).

(4) The patient has previously responded to duloxetine (Cymbalta).and changing to a formulary depression/non-opioid pain syndrome agent would incur unacceptable risk.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows: The existing MN criteria are approved as the manual (paper) PA criteria. The Pharmacoeconomic Center staff may make minor changes, NOT involving changes to the underlying criteria, to prior authorization forms, such as correcting contact information or rewording clinical questions, without further involvement of the DoD P&T Committee and the Beneficiary Advisory Panel and without further approval of the Director, TMA.

6. ***COMMITTEE ACTION: MILACIPRAN (SAVELLA) PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that milnacipran (Savella) be designated non-step-preferred requiring a trial of any non-opioid pain syndrome agent [Group C drug—SNRI, including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has filled a prescription for any non-opioid pain syndrome agent (Group C) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met: PA criteria will be developed from existing MN criteria. . The existing MN criteria are as follows:

(1) Use of the formulary non-opioid pain syndrome agents is contraindicated.

(2) The patient has experienced adverse effects from the formulary non-opioid pain syndrome agents.

(3) Use of the formulary non-opioid pain syndrome agents has resulted in therapeutic failure.

(4) The patient has previously responded to milnacipran (Savella) and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows: The existing MN criteria are approved as the manual (paper) PA criteria. The Pharmacoeconomic Center staff may make minor changes, NOT involving changes to the underlying criteria, to prior authorization forms, such as correcting contact information or rewording clinical questions, without further involvement of the DoD P&T Committee and the Beneficiary Advisory Panel and without further approval of the Director, TMA.

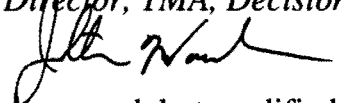
7. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical and cost evaluation of the Depression/Non-Opioid Pain Syndrome agents, and the conditions for establishing MN for a NF medication, the P&T Committee recommended (17 for, 0 opposed, 1 abstained, 1 absent) maintaining the current MN criteria for bupropion HBr (Aplenzin); desvenlafaxine (Pristiq); duloxetine (Cymbalta); milnacipran (Savella); pregabalin (Lyrica); and, until cost-effective generics become available, escitalopram (Lexapro); fluoxetine in special packaging (Sarafem), and fluoxetine weekly (Prozac weekly). The P&T Committee also recommended MN criteria for trazodone ER (Oleptro) and vilazodone (Viibryd). (See Appendix C for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

8. ***COMMITTEE ACTION: UF AND MN IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April 18, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved



Approved, but modified as follows:

B. Short-Acting Beta Agonists (SABAs)

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the inhaled Short-Acting Beta Agonists (SABAs). There are three SABA products marketed in the United States, which are formulated as pressurized metered dose inhalers (MDIs) or solutions for inhalation: albuterol (a racemic mixture), levalbuterol (the (R)-enantiomer form of albuterol), and pirbuterol. The SABA inhaled solutions include albuterol (Accuneb, generics; various concentrations), and levalbuterol (Xopenex).

Hydrofluoroalkane (HFA) replaced chlorofluorocarbon (CFC) as the propellant in albuterol MDIs in December 2008. The SABA MDI formulations include albuterol HFA (Ventolin HFA, Proventil HFA, ProAir), levalbuterol HFA (Xopenex), and pirbuterol (Maxair). Pirbuterol (Maxair) is the sole remaining CFC MDI on the market, and will be discontinued in December 2013. The three albuterol HFA products are not considered therapeutically interchangeable by the FDA.

The SABA drug class was previously reviewed for UF placement in November 2008. In fiscal year 2011, over $43M was spent on the SABAs at all three points of service in the MHS.

Information regarding the safety, effectiveness, and clinical outcomes of the SABAs was considered by the Committee. The clinical effectiveness review for the SABAs was limited to the outpatient setting; emergency department use was evaluated only when pertinent.

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (18 for, 0 against, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

1. In terms of efficacy/clinical effectiveness, there is little evidence to suggest there are clinically relevant differences between the SABAs for their FDA-

approved indications. There is no new significant information to change the clinical effectiveness conclusion from the November 2008 UF review.

- Evidence-based guidelines from the VA/DoD Clinical Practice Group (updated 2009), Global Initiative for Asthma, National Heart, Lung and Blood Institute/National Asthma Education & Prevention Program, and Global Initiative for Chronic Obstructive Lung Disease do not list a preference for one SABA over another for treating asthma, exercise-induced bronchospasm (EIB) or chronic obstructive pulmonary disease (COPD).
- For asthma, all the SABAs are more efficacious than placebo at improving the change in forced expiratory volume in one second $\geq$ 12% from baseline, whether administered via MDI or inhalational solution.
- There are no head-to-head studies comparing albuterol MDI with levalbuterol (Xopenex) MDI in adults or children.
- For adults with asthma, there is little evidence to suggest there are clinically relevant differences between albuterol and levalbuterol when administered via the nebulized route in either the outpatient or emergency department settings—in terms of number of puffs of rescue medication used daily or from hospitalization admission rates.
- For children with asthma, there are conflicting and inconclusive results as to whether there are efficacy differences between albuterol and levalbuterol inhalation solution when administered in the outpatient setting or emergency department.
- EIB—Placebo-controlled trials with albuterol administered via MDI 15 to 30 minutes before exercise reported statistically significant results in terms of preventing exercise-related symptoms compared to placebo. Although levalbuterol MDI (Xopenex) is not currently approved by the FDA for EIB, the results of placebo-controlled phase III trials do not suggest that the effect of levalbuterol at preventing EIB symptoms would differ from albuterol.
- COPD—There is insufficient evidence to compare the SABAs when used in COPD.

2. With regards to safety/tolerability, the following conclusions were made:
   - SABAs are associated with similar systemic adverse effects. A systematic review found no clinically relevant differences in discontinuation rates due to changes in heart rate, blood pressure, palpitations, nervousness, anxiety, tremor, hyperglycemia or hypokalemia between albuterol and levalbuterol inhalation solution.

- In the outpatient setting, in adults and children, the incidence of the withdrawal rates due to AEs and overall AE rates were similar between albuterol and levalbuterol inhaled solutions. However, in children there is insufficient evidence from the outpatient studies to determine whether there are clinically relevant differences in the incidence of tachycardia, as conflicting results were reported.
- There is insufficient data with the SABA MDI formulations to assess safety differences between albuterol and levalbuterol.

3. With regards to differences between the SABAs in terms of other factors, the following conclusions were made:
    - Special populations—The P&T Committee recognized that the FDA-approved pediatric age ranges differ between the products.
    - HFA formulations—There are only minor differences between the HFA formulations of albuterol and levalbuterol, including presence of a dose counter (Ventolin HFA is the only product with a dose counter), requirements for priming, storage conditions, and excipients (Ventolin HFA is the only SABA that does not contain alcohol). However, per FDA ruling, the HFA albuterol agents are not interchangeable.
    - Delivery devices—The Ventolin MDI is not compatible with the Lever Haler spacer, but is compatible with all other spacer devices.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the SABAs Drug Class. Based on the clinical findings regarding efficacy, safety, tolerability, and clinical outcomes with SABAs, cost-minimization analyses (CMAs) were performed to compare the metered-dose inhalers (MDIs) and inhalation solutions. Additionally, a BIA was performed to compare competing formulary scenarios for the MDIs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA results with the SABAs MDIs showed albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA) inhalers are most cost-effective. While levalbuterol (Xopenex) is comparable to albuterol HFA with regards to cost, pirbuterol (Maxair) is not cost-effective relative to the other MDIs in the class. BIA results indicated that pirbuterol (Maxair) MDI designated with NF status on the UF was the most cost-effective scenario for the MHS. When the inhalation solutions were compared, albuterol (generic; 2.5 mg/3mL concentration) was the most cost-effective inhalation solution.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0

opposed, 1 abstained, 0 absent) that the most cost-effective scenario designated albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA), levalbuterol HFA (Xopenex HFA), albuterol inhalation solution (Accuneb, generics), and levalbuterol inhalation solution (Xopenex) with formulary status on the UF and pirbuterol CFC (Maxair) inhaler with NF status on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA), levalbuterol HFA (Xopenex HFA), albuterol inhlation solution (Accuneb, generics), and levalbuterol inhalation solution (Xopenex) remain formulary on the UF. The P&T Committee recommended that pirbuterol CFC inhaler (Maxair) be designated NF on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

☐ Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) albuterol HFA (Ventolin HFA) and albuterol inhalation solution (generic; 2.5mg/0.5mL concentration) be designated with BCF status.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

☐ Approved, but modified as follows:

C. Phosphodiesterase Type-5 (PDE-5) Inhibitors for Erectile Dysfunction (ED)

The P&T Committee evaluated the cost-effectiveness analysis for the PDE-5 inhibitors for ED at an interim telephonic meeting held on December 15, 2011. The attendance roster for the interim meeting is found in Appendix B. Please refer to the August 2011 P&T Committee minutes for the relative clinical effectiveness review and conclusions.

Relative Cost Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the PDE-5 inhibitors sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra, Staxyn) for erectile dysfunction. Based on clinical findings regarding efficacy, safety, tolerability, other relevant factors, and clinical outcomes with these agents, CMAs were performed to compare individual agents. BIAs were also performed to compare competing formulary scenarios.

During this drug class evaluation, the DoD joined the VA in a joint national contracting effort. Sildenafil (Viagra) was selected as the winner of the VA/DoD national contract. To comply with the terms of the joint national contract, all scenarios considered in this review included sildenafil (Viagra) as a UF and BCF agent with all other agents designated NF.

Relative Cost Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (11 for, 0 opposed, 0 abstained, 0 absent) the following for the PDE-5 inhibitors:

- CMA results showed that sildenafil (Viagra) was the most cost-effective agent across all three points of service.

- BIA was used to compare the potential impact of discontinuing the current step therapy program (which requires a trial of vardenafil for new users with prescriptions for sildenafil or tadalafil) with scenarios where step therapy was maintained, but sildenafil (Viagra) replaced vardenafil as the step-preferred agent. Additional formulary scenarios evaluating the impact of implementing new retail restrictions were also considered. BIA results showed that, among currently available formulary options, the most cost-effective scenario placed sildenafil (Viagra) on the BCF and as the step-preferred product on the UF, with vardenafil (Levitra, Staxyn) and tadalafil (Cialis) designated NF and non-step preferred. Sensitivity analysis results supported the above conclusion.

- The P&T Committee discussed a potential program designed to strongly encourage the use of mail order instead of retail, for appropriate medications. The P&T Committee concluded that the PDE-5s would be well-suited to such a program clinically and including this drug class in such a program, if it becomes available, would most likely generate additional cost avoidance.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (11 for, 0 opposed, 0 abstained, 0 absent):

a) Sildenafil (Viagra 25 mg, 50 mg, and 100 mg) be designated with formulary status on the UF.

b) Tadalafil (Cialis 2.5 mg, 5 mg, 10 mg, and 20 mg) and vardenafil (Levitra 2.5 mg, 5 mg, 10 mg, and 20 mg; Staxyn 10 mg) be designated NF on the UF, based on cost-effectiveness.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (11 for, 0 opposed, 0 abstained, 0 absent) to recommend that sildenafil (Viagra 25 mg, 50 mg, and 100 mg) tablets be designated with BCF status immediately on signing of the November 2011 P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of tadalafil (Cialis) and vardenafil (Levitra and Staxyn) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) MN criteria for Cialis, Levitra, and Staxyn. (See Appendix C for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all

points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is April 18, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: STEP THERAPYAND PA CRITERIA***—The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) that step therapy apply to the PDE-5 inhibitors for the treatment of ED. For all new users of PDE-5 inhibitors, the following criteria apply:

   a) Automated Criteria:
   Coverage approved for treatment of ED if:
      (i) The patient has received a prescription for sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra and Staxyn) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days, AND
      (ii) The patient is a male aged 40 years or older.

   b) Manual Criteria:

   Coverage approved if:

      (i) Patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.

      (ii) Treatment with sildenafil (Viagra) is contraindicated.

      (iii) Patient is less than 40 years of age and is being treated for ED of organic or mixed organic/psychogenic origin. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in b) (i) or b) (ii)].

      (iv) Patient is less than 40 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in b) (i) or b) (ii)].

Coverage approved for the following non-ED uses requiring daily therapy:

(v) Use of tadalafil (Cialis or Adcirca) for Pulmonary Arterial Hypertension (PAH)

(vi) Use of any PDE-5 inhibitor for preservation/restoration of erectile function after prostatectomy

(vii) Use of any PDE-5 inhibitor for Raynaud's Phenomenon

(viii) Use of Cialis 5 mg for treatment of benign prostatic hyperplasia (BPH)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

6. ***COMMITTEE ACTION: PA IMPLEMENTATION PLAN***—The P&T Committee voted (11 for, 0 opposed, 0 abstained, 0 absent) to recommend the PA implementation plan be timed to coincide with that established for the UF decision for tadalafil and vardenafil.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

7. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee considered QLs for the treatment of ED as well as QLs for other indications. Based on the results of the clinical and economic evaluations presented, the P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) the following QLs:

Treatment of ED:

Mail Order: Collective QL of 18 tablets per 90 days

Retail: Collective QL of 6 tablets per 30 days

Daily therapy for the approved indications (PAH, preservation or restoration of erectile function after prostatectomy, Raynaud's Phenomenon and BPH):

Mail Order: 90-days supply

Retail: 30-days supply

Director, TMA, Decision: ☒Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. Tadalafil (Cialis)—PA: The PDE-5 inhibitor tadalafil (Cialis) 5 mg received FDA approval in October 2011 for treatment of BPH and ED with BPH. All PDE-5 inhibitors are currently subject to prior authorization, step therapy, quantity limits, and MN criteria. Prior authorization and step therapy also apply to the alpha-1 blockers used for BPH.

The DoD P&T Committee reviewed the clinical efficacy of tadalafil for BPH. Although the efficacy of tadalafil and the alpha-1 blockers for BPH cannot be directly compared, alpha-1 blockers provide relief of BPH urinary symptoms to a greater extent than PDE-5 inhibitors, based on changes from baseline in the International Prostate Symptom Scale reported in clinical trials. The P&T Committee also recommended that trial of a preferred alpha-1 blocker would be required for new users of tadalafil for BPH.

1. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) in addition to the existing PDE-5 inhibitors automated and manual PA criteria, the following PA criteria should also apply to the tadalafil when used for BPH:

a) Manual PA criteria:

(1) Patient is being treated for BPH and the dosing regimen prescribed is tadalafil 5 mg once daily AND

(a) The patient has tried tamsulosin or alfuzosin and had an inadequate response;

OR

(b) The patient has tried tamsulosin or alfuzosin and was unable to tolerate them due to adverse effects;

OR

(c) Treatment with tamsulosin or alfuzosin is contraindicated.

(d) Prior authorization for the BPH indication will expire after 1 year from input date.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: Tadalafil PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date upon signing of the November 2011 P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Tramadol ER (Conzip)—QLs: Conzip is a new tramadol ER formulation. It is FDA-approved for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain. QLs are currently in place for other tramadol ER formulations (Ultram ER, Ryzolt, generics), which are consistent with their product labeling.

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (15 for, 0 against, 1 abstain, 2 absent) QLs of 90 capsules /90 days in the mail order pharmacy and 30 capsules/30 days in the retail network, which is consistent with the recommended dosing from the product labeling.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Sunitinib malate (Sutent)—QLs: In May 2011, Sunitinib malate was FDA-approved for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease. The manufacturer's dosing recommendation includes the following regimen: 37.5 mg orally once daily, continuously without a scheduled off-treatment period.

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (15 for, 0 against, 1 abstain, 2 absent) the following QLs for sunitinib malate (Sutent):

Retail:

12.5mg: 120 caps/30 days
25mg: 60 caps/30 days
50mg: 30 caps/30 days

Mail:

12.5mg: 252 caps/84 days
25mg: 120 caps/84 days
50mg: 60 caps/84 days

The above QLs are consistent with the recommended dosing from the product labeling.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Abatacept (Orencia)—PA: A subcutaneous injection of abatacept (Orencia) has been marketed. Orencia will be reviewed as a new FDA-approved drug in the Targeted Immunomodulatory Biologics (TIBs) Drug Class at an upcoming DoD P&T Committee meeting. PA requirements apply to the other TIBs in the UF. The P&T Committee

agreed that the following PA criteria should apply to Orencia, consistent with the FDA-approved labeling and PA requirements for the other TIBs.

1. Coverage would be approved for the treatment of adult patients with moderate to severely active rheumatoid arthritis.
2. Coverage would not be provided for concomitant use with adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi), or rituximab (Rituxan).

a) ***COMMITTEE ACTION: PA***—The P&T Committee recommended (15 for, 0 against, 1 abstain, 2 absent) approving the PA criteria outlined above.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

E. Abatacept (Orencia)—QLs: QLs are currently in place for the TIBs, which are consistent with the product labeling.

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (15 for, 0 against, 1 abstain, 2 absent) QLs of 8 syringes/56 days in the mail order pharmacy and 4 syringes/28 days in the retail network, which is consistent with the recommended dosing from the product labeling and avoids wastage.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VII. ITEMS FOR INFORMATION

A. Antilipidemic-1s (LIP-1s)—Clarification of PA criteria: In May 2010, the P&T Committee recommended step therapy and PA criteria for the LIP-1s Drug Class, and designated generic statins and atorvastatin (Lipitor) as step-preferred drugs within the class. Since implementation, an audit revealed the need to clarify the manual PA

criteria. The P&T Committee recommended clarifications to the manual PA criteria to accurately reflect their intent.

VIII. CLASS OVERVIEWS

Three drug class overviews were presented to the P&T Committee. The Attention Deficit Hyperactivity Disorder and Narcolepsy Drug Class was last reviewed in November 2006. The Dipeptidyl-Peptidase 4 Inhibitors Drug Class was presented in November 2010 as part of the Non-Insulin Diabetes Drug Class. Information regarding antiplatelet drugs was also presented; this drug class has never been reviewed. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost-effectiveness models. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

IX. ADJOURNMENT

The meeting adjourned at 1710 hours on November 9, 2011. An interim telephonic follow-on meeting was held on December 15, 2011. The next meeting will be in February 2012.

Appendix A—Attendance: November 2011 P&T Committee Meeting

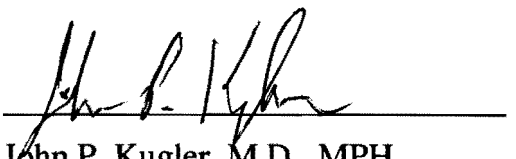
Appendix B—Attendance: December 15, 2011 Interim Meeting

Appendix C—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Appendix E—Table of Abbreviations

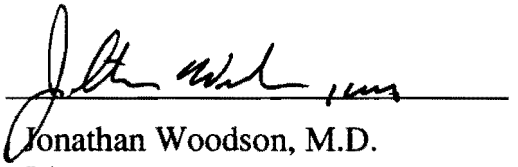
SUBMITTED BY:



John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.



Jonathan Woodson, M.D.
Director

7 Feb. 2012
(Date)

Appendix A—Attendance: November 2011 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
LTC Ric Nannini for COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Dennis Alder	Coast Guard, Pharmacy Officer
CAPT Edward Norton	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT David Tanen, MC	Navy, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
LTC Jack Lewi for COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
LTC Daniel Hsu for COL Ted Cieslak, MC	Army, Physician at Large
LTC Bruce Lovins, MC	Army, Family Practice Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
Dr. Miguel Montalvo	TRICARE® Regional Office-South Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
CDR Jay Peloquin	Defense Logistics Agency Troop Support
Guests	
Dr. Warren Lockette	Chief Medical Officer, TRICARE Management Activity

Appendix A—Attendance: November 2011 P&T Committee Meeting (continued)

Guests	
COL Todd Williams	Defense Medical Materiel Program Office
CDR Mike Lee	Indian Health Service
Capt Justin Lusk	AMEDD Center and School
Dr. Vincent Calabrese	Department of Veterans Affairs
Ronda Wenzel	University of Incarnate Word Pharmacy Intern
Ellen Tsay	University of Maryland Pharmacy Intern
Others Present	
Lt Col Rey Morales	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
MAJ Misty Cowan	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Maj David Folmar	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo via teleconference	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Bradley Clarkson	Pharmacy Resident

Appendix B—Attendance: December 15, 2011 Interim Meeting

Voting Members Present via DCO	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
LTC Ric Nannini for COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Edward Norton	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
Col Lowell Sensintaffer, MC	Air Force, Physician at Large
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
LTC Bruce Lovins, MC	Army, Family Practice Physician
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Dr. Miguel Montalvo	TRICARE® Regional Office-South Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present via DCO	
Mr. David Hurt	Associate General Counsel, TMA
Others Present	
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Maj David Folmar	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Angela Allerman via DCO	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe via DCO	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Attendance December 15, 2011 Interim Meeting (continued)

Others Present	
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Bradley Clarkson	Pharmacy Resident

Appendix C—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Risedronate delayed release (Atelvia) **Osteoporosis Agents**	• Use of risedronate IR, ibandronate oral, and alendronate is contraindicated. • Patient has experienced significant adverse effects from risedronate IR, ibandronate oral, and alendronate.
Trazodone extended release (Oleptro) **Depression / Non-Opioid Pain Syndrome Agents**	• Use of the formulary depression/non-opioid pain syndrome agents is contraindicated.
Vilazodone (Viibryd) **Depression / Non-Opioid Pain Syndrome Agents**	• No alternative formulary agent – patient requires a drug with activity as serotonin-1a partial agonist/reuptake inhibitor and is unable to tolerate buspirone plus a selective serotonin reuptake inhibitor.
Tadalafil (Cialis) **PDE-5 Inhibitors**	• Use of Viagra is contraindicated • Patient has experienced significant adverse effects from Viagra • Viagra has resulted in therapeutic failure
Vardenafil (Levitra, Staxyn) **PDE-5 Inhibitors**	• Use of Viagra is contraindicated • Patient has experienced significant adverse effects from Viagra • Viagra has resulted in therapeutic failure

Appendix D—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2011	**Depression and Non-Opioid Pain Syndrome Agents**	UF Class Review	**SSRIs:** citalopram fluoxetine sertraline **SNRIs:** venlafaxine IR venlafaxine ER **SPARIs:** trazodone **NDRIs:** bupropion HCl IR bupropion HCl SR bupropion HCl ER **GABA analogs:** gabapentin **TCAs:** amitriptyline doxepin imipramine HCl nortriptyline	**SSRIs:** citalopram fluoxetine fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate sertraline **SNRIs:** venlafaxine IR venlafaxine ER venlafaxine ER tablets **SARIs:** nefazodone trazodone **NDRIs:** bupropion HCl IR bupropion HCl SR bupropion HCl ER **TCAs:** amitriptyline desipramine doxepin imipramine HCl imipramine pamoate nortriptyline protriptyline **A2RAs:** mirtazapine tablets mirtazapine ODT **GABA analogs:** gabapentin	**SSRIs:** escitalopram (Lexapro) fluoexetine (Sarafem) fluoxetine weekly (Prozac Weekly) **SNRIs:** desvenlafaxine (Pristiq) duloxetine (Cymbalta) milnacipran (Savella) **SARIs:** trazodone ER (Oleptro) **SPARIs:** vilazodone (Viibryd) **NDRIs:** bupropion HBr (Aplenzin) **GABA analogs:** pregabalin (Lyrica)	Pending signing of minutes/ 60 days	Step therapy (Automated PA)	Step therapy will apply for four agents in this class: Pristiq is NF and non step-preferred. All new users of Pristiq are required to try venlafaxine first. Cymbalta is NF and non step-preferred. All new users of Cymbalta are required to try an antidepressant (Group B drug) or non-opioid pain syndrome agent (Group C) first. Savella is NF and non step-preferred. All new users of Savella are required to try a non-opioid pain syndrome agent (Group C) first. Lyrica is NF and non step-preferred. All new users of Lyrica are required to try gabapentin first.

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2011	**Short Acting Beta Agonists (SABAs)**	UF Class Review	No change from previous review November 2008 • albuterol nebulizing solution (0.083% [2.5 mg/3 mL]) • Ventolin HFA MDI	• albuterol nebulizing solution (0.5% [2.5 mg/0.5 mL] • albuterol nebulizing solution (Accuneb) • Proair HFA • Proventil HFA • Levalbuterol HFA (Xopenex HFA) • Levalbuterol nebulzing solution (Xopenex) • Ventolin HFA MDI	• pirbuterol CFC (Maxair)	Not Applicable	Existing QLs apply	-
Nov 2011	**Phosphodiesterase -5 (PDE-5) Inhibitors for Erectile Dysfunction (ED)**	UF Class Review	• sildenafil (Viagra)	• sildenafil (Viagra)	• tadalafil (Cialis) • vardenafil (Levitra, Staxyn)	Pending signing of minutes/ 60 days	Step therap y (Automated PA) and QLs apply	Viagra is BCF and step-preferred. Cialis and Levitra are NF and non step-preferred
Nov 2011	**Osteoporosis Agents** **Subclass: bisphosphonates**	New Drug in Already Reviewed Class	No change from previous review June 2008 • alendronate • alendronate with Vitamin D • ibandronate	• alendronate • alendronate with Vitamin D • ibandronate • risedronate IR (Actonel) • risedronate IR with calcium (Actonel with Calcium)	• risedronate DR (Atelvia)	Pending signing of minutes/ 60 days	-	-

Group B drugs: SSRIs, SNRIs (except milnacipran), TCAs, mirtazapine, bupropion, SARIs, or MAOIs
Group C drugs: SNRIs including milnacipran, TCAs, cyclobenzaprine, gabapentin or pregabalin

CFC: chlorofluorocarbon
DR: delayed release
ER: extended release
HFA: hydrofluoroalkane
IR: immediate release
QLs: quantity limits

Appendix E—Table of Abbreviations

AEs	adverse events
A2RAs	alpha-2 receptor antagonists
BCF	Basic Core Formulary
BPH	benign prostatic hypertrophy
BIA	budget impact analysis
CFC	chlorofluorocarbon
CFR	Code of Federal Regulations
CLBP	chronic low back pain
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DoD	Department of Defense
DERP	Oregon Drug Effectiveness Review Project
DPN	diabetic peripheral neuropathy
DR	delayed release
ED	erectile dysfunction
EIB	exercise-induced bronchospasm
ER	extended release
FM	Fibromyalgia
FDA	U.S. Food and Drug Administration
GABA	gamma-aminobutyric acid
CGI	Clinical Global Impression
HFA	Hydrofluoroalkane
HRQoL	health-related quality of life
IR	Immediate release
MDD	major depressive disorder
MHS	Military Health System
MN	medical necessity
MDIs	metered-dose inhalers
MTF	Military Treatment Facility
NF	Nonformulary
NDRIs	norepinephrine/dopamine reuptake inhibitors
NSAIDs	non-steroidal anti-inflammatory drugs
ODT	orally dissolving tablets
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAH	pulmonary artery hypertension
PEC	Pharmacoeconomic Center
PDE-5	phosphodiesterase type-5 inhibitor
PORT	Pharmaceutical Outcomes Research Team
PHN	post-herpetic neuralgia
QLs	quantity limits
SABAs	Short-Acting Beta Agonists
SSRIs	selective serotonin reuptake inhibitors
SNRIs	selective serotonin/norepinephrine reuptake inhibitors
SARIs	serotonin antagonist reuptake inhibitors
SPARIs	serotonin partial agonist/reuptake inhibitors
TIBs	Targeted Immunomodulatory Biologics
UF	Uniform Formulary
VA	U.S. Department of Veterans Affairs

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
August 2011

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 10 and 11, 2011, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May Minutes**—Jonathon Woodson M.D. Director, approved the minutes for the May 2011 DoD P&T Committee meeting on August 5, 2011.
2. **Addendum to the May Minutes**—Jonathon Woodson M.D. ASD(HA) also approved on August 5, 2011 the retail network and mail order pharmacy co-pay changes for tiers 1(generic), 2 (formulary) and 3 (non-formulary) and for retail non-network pharmacies, which are effective October 1, 2011.

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Renin Angiotensin Antihypertensives (RAAs)—Azilsartan (Edarbi)

Relative Clinical Effectiveness—Azilsartan (Edarbi) is a once daily angiotensin receptor blocker (ARB), the eighth ARB to enter the market. It is classified in the RAAs drug class. The class was last reviewed in August 2010. The clinical evaluation for Edarbi included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Edarbi is indicated for the management of hypertension, alone or in combination with other agents. It has no other FDA-approved indications and there are no clinical outcomes (e.g., reduction in heart failure hospitalization, death, or type 2 diabetic renal disease) studies completed, in-process, or planned. Because of corresponding published reductions in stroke and all-cause mortality, a reduction of either systolic or diastolic blood pressure (BP) of 2 mm Hg or more is considered clinically meaningful for this review.

In seven clinical trials—two published and five unpublished—Edarbi demonstrated efficacy in treating hypertension. In two studies, it demonstrated superiority to valsartan

(Diovan), a step-preferred, basic core formulary (BCF) agent, at a clinically meaningful reduction in systolic BP of 3-5 mm Hg. Additionally, Edarbi showed non-inferiority and statistical superiority (and a potentially clinically meaningful systolic BP reduction of 1-2 mm Hg) to olmesartan (Benicar). In terms of safety, there is no evidence that Edarbi is more or less safe, on average, than any of the seven other ARBs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) azilsartan (Edarbi) offers a compelling therapeutic advantage over valsartan and possibly olmesartan, but does not have clinical outcomes studies available.

Relative Cost-Effectiveness—Although the clinical review concluded Edarbi produced a clinically relevant reduction in BP compared to other ARBs, cost-minimization analysis (CMA) was used to compare its cost to the other ARBs, consistent with the cost analysis for the ARBs subclass conducted at the August 2010 UF review for the RAAS. CMA was performed to evaluate Edarbi's cost in comparison to other UF RAAs drugs, including generic losartan, telmisartan (Micardis), valsartan (Diovan), irbesartan (Avapro), olmesartan (Benicar), and candesartan (Atacand). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that Edarbi was more costly than telmisartan (Micardis), valsartan (Diovan), irbesartan (Avapro), olmesartan (Benicar), and less costly than Atacand (candesartan).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 1 abstained, 1 absent) azilsartan (Edarbi) remain formulary on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 1 abstained, 1 absent) azilsartan (Edarbi) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) that azilsartan (Edarbi) be designated non-step preferred requiring the following step-therapy/PA criteria. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any Military Health Service (MHS) pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

      (2) The patient has received a prescription for azilsartan (Edarbi) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

      (2) The patient has tried one of the preferred RAAs and has had an inadequate response.

(3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is January 4, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

B. RAAs—Aliskiren/Amlodipine/Hydrochlorothiazide (Amturnide)

Relative Clinical Effectiveness—Amturnide is a once daily triple-fixed dose combination (FDC) antihypertensive product. It contains aliskiren, a direct renin inhibitor (DRI), amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and hydrochlorothiazide (HCTZ), a thiazide-type diuretic. Amturnide is the third triple-combination antihypertensive to enter the market. It is classified in the RAAs drug class due to the aliskiren (DRI) component. This class was last reviewed in August 2010. The clinical evaluation for Amturnide included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Amturnide is indicated for the management of hypertension as an add-on or switch from two of the components, or as a substitute for all three titrated components, but not for initial therapy. It has no other FDA-approved indications and there are no clinical outcomes studies completed, in-process, or planned. Aliskiren has outcomes studies underway, while amlodipine and HCTZ have well-established published outcomes data.

In three unpublished clinical trials, Amturnide demonstrated efficacy in treating hypertension versus the efficacy demonstrated by dual combinations of the individual component medications. In terms of safety, there is no evidence that Amturnide is more or less safe, on average, than either of the two other triple FDCs,

valsartan/amlodipine/HCTZ (Exforge HCT) and olmesartan/amlodipine/HCTZ (Tribenzor). The combination of these three drug classes (DRI, DHP CCB and thiazide diuretic) has no compelling advantage in terms of efficacy over giving other combinations (e.g., ARB/DHP CCB/HCTZ). In terms of safety, the Amturnide FDC partially offsets the peripheral edema common to CCBs, the hypokalemia common to diuretics, and the hyperkalemia sometimes seen with ARBs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that Amturnide does not offer a compelling therapeutic advantage in terms of efficacy or safety over other antihypertensive FDCs currently on the UF.

Relative Cost-Effectiveness—CMA was performed to evaluate the cost of aliskiren/amlodipine/HCTZ (Amturnide) in relation to the other UF RAAs drugs, including the following: aliskiren/HCTZ (Tekturna HCT) plus generic amlodipine, benazepril/amlodipine, telmisartan/amlodipine (Twynsta), olmesartan/HCTZ (Benicar HCT), valsartan/amlodipine (Exforge), valsartan/amlodipine/HCTZ (Exforge HCT), olmesartan/amlodipine (Azor), and olmesartan/amlodipine/HCTZ (Tribenzor). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (13 for, 0 opposed, 0 abstained, 2 absent) Amturnide was more costly than Exforge (valsartan containing triple FDC), but less costly than Tribenzor (olmesartan containing FDC).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 0 opposed, 1 abstained, 2 absent) aliskiren/amlodipine/HCTZ (Amturnide) remain formulary on the UF, as the FDC of DRI/amlodipine/HCTZ may be necessary for hypertensive patients requiring 3 drugs who do not respond to other triple FDC RAAs.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 0 opposed, 1 abstained, 2 absent) aliskiren/amlodipine/HCTZ (Amturnide) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) aliskiren/amlodipine/HCTZ (Amturnide) be designated non-step preferred requiring the following step-therapy/PA criteria. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

      (2) The patient has received a prescription for aliskiren/amlodipine/HCTZ (Amturnide) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

(2) The patient has tried one of the preferred RAAs and has had an inadequate response.

(3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is January 4, 2012.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows

C. Non-Insulin Diabetes Drugs Dopamine Agonist—Bromocriptine Mesylate (Cycloset)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of a newly approved formulation of bromocriptine, bromocriptine mesylate (Cycloset). The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Cycloset is a centrally-acting dopamine agonist (DA) and is the only DA approved for the treatment of diabetes. This agent falls into the new DA subclass of the Non-Insulin Diabetes Drugs, which was reviewed for UF placement in November 2010. The other subclasses include dipeptidyl-peptidase 4 inhibitors (DPP-4s), thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists biguanides, sulfonylureas (SUs), meglitinides, and alpha-glucosidase inhibitors. Step therapy (automated PA) applies for the Non-Insulin Diabetes Drug Class, which requires a trial of metformin or a sulfonylurea.

Bromocriptine is an old drug with a new use. It was first approved in 1978 for the treatment of Parkinson's disease and has uses in other endocrine-related disorders such as hyperprolactinemia, acromegaly, and prolactin-secreting adenomas. Bromocriptine should not be used to suppress lactation since an increase in stroke and myocardial infarction were reported in postpartum women. The new bromocriptine Cycloset product is a quick release formulation administered in the morning. Other bromocriptine mesylate formulations are available, including immediate release (IR) 2.5 tablets and scored tablets, and 5 mg IR capsules (Parlodel, generics). Decreased levels of dopamine may contribute to insulin resistance, and increasing dopamine activity in the morning is effective at improving glucose dysregulation. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for bromocriptine mesylate (Cycloset):

- Uptitration of Cycloset is required to achieve the maximum therapeutic benefit. Patients start with 0.8mg (1 tab) daily and increase by 0.8mg in weekly increments to a maximally tolerated dose of 4.8mg daily. The minimum therapeutic dose is 1.6mg daily.

- When used as monotherapy, Cycloset decreased glycosolated hemoglobin or hemoglobin A1c (HbA1c) 0.1% from baseline compared to placebo. Cycloset decreased HbA1c 0.1-0.4% from baseline when added to a SU and a produced a maximum 0.5% decrease from baseline when combined with both metformin and a SU.

- There are no head-to-head studies to date with other non-insulin diabetes medications and no long-term outcomes studies currently in progress.

- Bromocriptine mesylate is weight neutral; however, as with other medications, more weight gain is likely when administered with a SU or TZD. It may have a beneficial effect on lipid levels and BP.

- Nausea is the primary side effect (~31%) although bromocriptine mesylate is generally well tolerated. The incidence of serious adverse events is similar to placebo.

- There was a statistically significant decrease in major cardiovascular events with Cycloset noted in one 52-week study. However, the clinical relevance of this secondary endpoint is not clear.

- Many potential drug interactions exist with Cycloset, including strong CYP 3A4 inducers or inhibitors; highly protein-bound drugs (e.g. salicylates, sulfonamides, chloramphenicol, probenecid); dopamine receptor antagonists; ergot-related drugs and sympathomimetic drugs.

- According to current T2DM treatment guidelines, the place in therapy for bromocriptine mesylate (Cycloset) remains unknown.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of bromocriptine mesylate (Cycloset). CMA was performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e) (2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (13 for, 0 opposed, 0 abstained, 2 absent) Cycloset was more costly when compared to step-preferred UF agents (metformin, SU, DPP-4 inhibitors, TZDs) and generic bromocriptine mesylate IR.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 1 opposed, 1 abstained, 1 absent) bromocriptine mesylate (Cycloset) be designated NF and non-step preferred.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of bromocriptine mesylate (Cycloset) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) MN criteria for bromocriptine mesylate (Cycloset). (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—Step therapy applies to this new subclass (dopamine agonists) requiring prior trial of metformin or a sulfonylurea. Bromocriptine mesylate (Cycloset) is recommended to be designated as non-step preferred and NF. The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to bromocriptine mesylate (Cycloset).

   a) Automated PA criteria:

      (1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

      (2) The patient has received a prescription for bromocriptine mesylate (Cycloset) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has a confirmed diagnosis of T2DM.
      (2) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.
      (3) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.
      (4) The patient has a contraindication or has had inadequate therapy to both metformin and a SU.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this decision. Based on the P&T Committee's recommendation, the effective date is January 4, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Narcotic Analgesics—Buprenorphine Transdermal System (Butrans)

Relative Clinical Effectiveness—Butrans is a transdermal formulation of buprenorphine, a semi-synthetic opioid with mixed agonist/antagonist activity at opioid receptors. It is a Schedule III drug, classified as a low-potency single analgesic agent in the Narcotic Analgesics Drug Class. The class was last reviewed in February 2007. The clinical evaluation for Butrans included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

There are other formulations of buprenorphine commercially available: parenteral formulations for post-operative pain management and sublingual tablets for the management of opioid-dependence. Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock, opioid analgesic for an extended period of time. One transdermal system allows for systemic delivery of buprenorphine, continuously over seven days, which offers a convenient regimen for patients.

In two unpublished clinical trials, Butrans demonstrated efficacy in treating chronic low back pain. There are no direct head-to-head studies comparing it to other long-acting narcotic agents of similar potency marketed in the United States. In terms of safety, there are some additional concerns with Butrans compared to other narcotics, particularly the risk of QTc prolongation at doses greater than 20mcg/hr, which will limit its use in patients with unstable cardiac disease. The major safety issue with Butrans is buprenorphine-induced respiratory depression. This poses a concern for elderly patients or those with impaired pulmonary function since the effects of buprenorphine are not completely reversible with naloxone (an opioid antagonist). Butrans is not intended for patients requiring treatment with high–dose opioids (>80 mg/day of morphine or equivalent), another factor that may limit its use in patients stable on alternative opioid analgesics. Butrans provides an additional treatment option when a long-acting, low-potency analgesic is needed.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that other than the convenience of less frequent dosing, buprenorphine transdermal system (Butrans) offers no other compelling therapeutic advantages over the other low potency narcotic analgesics currently on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated Butran's cost relative to the other low-potency agents in the Narcotic Analgesics Drug Class. CMA was performed based on clinical findings that efficacy, safety, tolerability, and factors other than patient convenience found among the agents in this class were similar at equipotent doses. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e) (2).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, concluded (15 for, 0 opposed, 0 abstained, 0 absent) that buprenorphine transdermal system (Butrans) was more costly, based on an average weighted cost per day of therapy, than other low-potency single analgesic agents currently on the UF. However, Butrans was less costly than the sublingual formulations of buprenorphine already on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 2 opposed, 1 abstained, 0 absent) buprenorphine transdermal system (Butrans) remain formulary on the UF with prior authorization to ensure appropriate use of the drug.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 0 abstained, 0 absent) buprenorphine transdermal system (Butrans) be excluded from the BCF.

Director, TMA, Decision: ☑ Approved □ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to Butrans. Coverage would be approved if the patient met any of the following criteria:

    a) Manual PA criteria:

        (1) Coverage provided for patients ≥18 yrs with moderate-to-severe chronic pain requiring opioid therapy.

            (a) Opioid naïve patients (prior use of <30 mg/day of morphine or equivalent in past 60 days) are limited to Butrans 5 mcg/hr patch.

            (b) Opioid tolerant patients (prior use of 30mg/day to 80 mg/day of morphine or equivalent within past 60 days or Butrans 5 mcg/hr patch) can receive Butrans 10 mcg/hr and 20 mcg/hr patches.

            (c) Maximum dose of Butrans is 20 mcg/hr.

        (2) Coverage NOT provided for treatment of opioid-dependence.

        (3) Coverage NOT provided for patients:

            (a) Requiring >80 mg/day of morphine or equivalent for pain control;

            (b) With significant respiratory depression or severe bronchial asthma;

            (c) With long QT syndrome or family history of long QT syndrome;

            (d) On concurrent Class 1A (procainamide, quinidine) or Class III (dofetilide, amiodarone, sotalol) antiarrythmics.

Director, TMA, Decision: ☑ Approved □ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is January 4, 2012.

Director, TMA, Decision: ☑ Approved □ Disapproved

Approved, but modified as follows

IV. UF DRUG CLASS REVIEWS

A. Oral Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the oral NSAIDs. There are 26 drugs in the class, comprised of 19 different chemical entities. Generic formulations are available for 21 drugs and there are 5 branded products: Celebrex, Arthrotec, Vimovo, Zipsor, and Cambia. Celecoxib (Celebrex) is the only cyclooxygenase-2 (COX-2) selective inhibitor available in the United States. Two FDCs of an NSAID with an anti-ulcer drug are available. Arthrotec is a combination of diclofenac and the prostaglandin analog misoprostol. Vimovo is the first FDC of an NSAID and a proton pump inhibitor (PPI) and is comprised of naproxen and esomeprazole. Diclofenac potassium liquid-filled capsules (Zipsor) contains 25 mg of diclofenac potassium, which is the lowest diclofenac dosage strength marketed; it is solely indicated for relief of mild-to-moderate acute pain. Cambia is a formulation of diclofenac potassium in powder packets for suspension.

The partially COX-2-selective NSAIDs include meloxicam, nabumetone, and etodolac. The remaining drugs in the class are the non-COX-2-selective NSAIDs: diclofenac potassium tablets (Cataflam, generics), diclofenac sodium (Voltaren, generics), diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid (Ponstel, generics), naproxen (Naprosyn, generics),

naproxen sodium (Anaprox, generics), naproxen sodium extended release (ER) (Naprelan CR, generics), oxaprozin, piroxicam, sulindac, and tolmetin.

The oral NSAIDs have not previously been reviewed; however, prior to implementation of the Uniform Formulary Rule in 2005, the following drugs were added to the BCF: ibuprofen, indomethacin, meloxicam, and naproxen. The clinical review focused on use of the oral NSAIDs for adults with chronic pain due to osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis. The review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 1absent) the following conclusions for the Oral NSAIDs:

With regards to efficacy,

1. For short-term pain relief (less than 6 months), all of the oral NSAIDs have a similar effect on reducing chronic pain in adults due to osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis, based on systematic reviews from the Oregon Drug Effectiveness Review Project (DERP), and the Cochrane group.
2. There is no significant difference in efficacy of pain relief with celecoxib (Celebrex) versus the partially COX-2 selective or nonselective NSAIDs, based on results from randomized controlled trials, meta-analyses, and a systematic review from the Agency for Healthcare Research and Quality (AHRQ; Chou 2007).
3. Diclofenac potassium liquid-filled capsules (Zipsor) were superior to placebo for reducing pain following bunionectomy in two trials. There are no head-to-head trials comparing Zipsor to the other NSAIDs.
4. The FDC of naproxen with esomeprazole (Vimovo) was superior to placebo and non-inferior to celecoxib for reducing pain in patients with osteoarthritis of the knee in two trials.

With regard to gastrointestinal (GI) safety,

5. All the NSAIDs increase the risk of serious GI adverse reactions, including bleeding, inflammation, ulceration, and perforation of the stomach or intestines, which can be fatal.
6. Celecoxib showed benefit for short-term (therapy duration less than or equal to 6 months) GI safety versus nonselective NSAIDs based on meta-analyses (DERP and AHRQ) and the SUCCESS trial. However, celecoxib did not show benefit for long-term (therapy duration greater than 6 months) GI safety (CLASS trial; DERP and AHRQ meta-analyses; FDA analysis).
7. In one trial, celecoxib plus aspirin versus naproxen plus the PPI lansoprazole plus aspirin showed no significant difference for development

of endoscopically-confirmed ulcers at 12 weeks (short-term) (Goldstein 2007).

8. Celecoxib versus diclofenac plus the PPI omeprazole showed no significant differences in terms of recurrent ulcer bleeding at 6 months (short-term GI safety) (Chan 2002 New England Journal of Medicine).
9. The GI protective effects of celecoxib therapy alone versus NSAID plus PPI were recently evaluated in the CONDOR study. The results showed short-term GI safety benefit for celecoxib for the composite endpoint of upper and lower GI bleeds when compared to diclofenac plus omeprazole. The results were primarily due to a lower risk of a decrease in hemoglobin (due to presumed occult bleeding of GI origin in the small bowel) in the celecoxib group. (Chan 2010 Lancet)
10. For high-risk patients, taking celecoxib with a PPI may provide increased GI protection versus long-term celecoxib monotherapy. The results of one good-quality trial reported that celecoxib plus omeprazole significantly lowered recurrent GI bleeding in very high-risk GI patients (12-month trial) (Chan 2007 Lancet).
11. For the partially selective NSAIDs, nabumetone showed short-term GI safety benefit compared to nonselective NSAIDs in a single meta-analysis of fair quality (Huang 1999). Etodolac and meloxicam showed no consistent differences in conferring GI safety benefit as compared to nonselective NSAIDs, based on randomized controlled trials and observational studies.
12. For the non-COX-2-selective NSAIDs, clinical trial data suggest that all nonselective NSAIDs are associated with relatively similar risks of serious GI events.
13. Further study is needed to determine the comparative GI safety benefits of concomitant use of an NSAID with various gastroprotective agents (misoprostol, H2 blocker, PPI) in preventing clinical GI events. Misoprostol decreases the risk of clinically relevant GI events, but is associated with a significant increase in nausea, diarrhea, and abdominal pain.
14. In terms of endoscopically visualized gastric ulcers and discontinuation of therapy due to GI adverse events, Vimovo showed short-term GI safety benefit in patients taking low-dose aspirin versus enteric-coated naproxen alone in two trials.
15. There is insufficient data with Zipsor to assess GI risks.

With regard to cardiovascular (CV) safety,

16. NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal.
17. Based on indirect analyses and observational studies, naproxen appears to be risk-neutral with regard to cardiovascular events; however, a black box warning is still present in the package insert for CV events.
18. Celecoxib, partially-selective NSAIDs, and nonselective NSAIDs have an increased risk of CV events, but there are no consistent differences in the incidence of CV events between them (with the exception of naproxen), based on clinical trials, and the DERP and AHRQ analyses.
19. No CV events related to Vimovo and Zipsor were reported in short-term clinical trials, but there is limited data available.

With regard to tolerability,

20. Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs demonstrated improved or similar tolerability profiles. There are no clear differences in tolerability between the nonselective NSAIDs
21. Vimovo showed a significant benefit in tolerability as compared to use of enteric-coated naproxen alone.

With regard to other factors,

22. Two NSAIDs are available over-the-counter without a prescription: ibuprofen and naproxen.
23. Four NSAIDs are formulated as oral suspensions: indomethacin, meloxicam, ibuprofen, and naproxen.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the oral NSAIDs. Based on the clinical findings regarding efficacy, safety, tolerability, and clinical outcomes with NSAIDs, a CMA was performed to compare the non-COX-2 selective/partially-COX-2 selective NSAIDs and NSAID/anti-ulcer FDCs. A cost-effectiveness analysis (CEA) was conducted to compare celecoxib (Celebrex) with the nonselective NSAIDs for treatment of osteoarthritis, and a budget impact analysis (BIA) was performed to compare competing formulary scenarios. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA results for nonselective/partially-selective NSAIDs showed that these products are the most cost-effective option within the oral NSAID class and should be used prior to treatment with NSAID/anti-ulcer FDCs or celecoxib (Celebrex) when clinically appropriate. However, several specific

nonselective/partially-selective NSAIDs were recognized as not being cost-effective relative to the other agents in the class, including naproxen sodium ER (Naprelan CR, generic), diclofenac potassium liquid-filled capsules (Zipsor), diclofenac potassium powder packets (Cambia), and mefenamic acid (Ponstel, generic). The NSAID/anti-ulcer FDCs were comparable on costs with other agents in the oral NSAID class.

Results of the CEA demonstrated that celecoxib was more costly than the nonselective/partially-selective NSAIDs. Published clinical evidence suggested lower risk of GI events with celecoxib compared to nonselective NSAIDs in the short-term (less than or equal to 6 months). However, the cost of preventing an additional ulcer complication with celecoxib was high due to the large difference in cost and small risk reduction in the published clinical data with celecoxib compared to nonselective NSAIDs. Longer-term evidence (greater than 6 months) with celecoxib remains inconclusive with regards to GI risk. Based on these findings, celecoxib should be reserved for patients at high risk for adverse GI events.

The BIA compared several formulary scenarios, including a scenario with an automated PA (step therapy) requiring a trial of generic formulations of partially-selective or nonselective NSAIDs prior to use of celecoxib, and a scenario without an automated PA (no step therapy). The BIA results concluded that the no step-therapy scenario was more cost-effective than the scenario with step therapy for new users of celecoxib.

Relative Cost Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that the most cost-effective scenario designated the following with formulary status on the UF: diclofenac potassium, diclofenac sodium, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin, naproxen/esomeprazole (Vimovo), diclofenac/misoprostol (Arthrotec), and celecoxib (Celebrex).

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 1 abstained, 1 absent) the following remain formulary on the UF without step therapy: diclofenac potassium, diclofenac sodium, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin, naproxen/esomeprazole (Vimovo),

diclofenac/misoprostol (Arthrotec), and celecoxib (Celebrex). The P&T Committee recommended diclofenac potassium liquid-filled capsules (Zipsor), diclofenac potassium powder packets (Cambia), naproxen sodium ER (Naprelan CR), and mefenamic acid (Ponstel) be designated NF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

☐ Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 1 abstained, 1 absent), ibuprofen (400 mg, 600 mg, 800 mg tablets and ~~125 mg/5 mL suspension~~), indomethacin (25 mg, 50 mg), meloxicam (7.5 mg, 15 mg) and naproxen (250 mg, 500 mg) remain designated with BCF status.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

☐ Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical and cost evaluation of the oral NSAIDs and the conditions for establishing MN for a NF medication, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) MN criteria for diclofenac potassium liquid-filled capsules (Zipsor), diclofenac potassium powder packets (Cambia), naproxen sodium ER (Naprelan CR), and mefenamic acid (Ponstel). Since there are many formulary alternatives available, the MN criteria would require that a formulary alternative be contraindicated. (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

☐ Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 4, 2012

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Contraceptive Agents

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the drugs in the Contraceptive Agents class. The clinical review for the contraceptive products included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1). The Contraceptives Agents class is comprised of three subclasses: oral contraceptive products (OCPs), miscellaneous contraceptives (transdermal patch, vaginal ring, medroxyprogesterone injections) and emergency contraceptives. The subclasses are outlined in Table 1 on pages 30–33.

The Contraceptive Agents were previously reviewed in May 2006 for UF status. Generic formulations are available for several products (See Table 1). Four new OCPs have recently entered the market: drospirenone 3mg/ethinyl estradiol (EE) 20 mcg/levomefolate Ca 0.451mg (Beyaz), norethindrone acetate 1mg/EE 10mcg/ferrous fumerate 75mg (Lo Loestrin Fe), levonorgesterol 0.1mg/EE 20mcg and levonorgesterol 0.1mg/EE 10mcg for extended use (LoSeasonique), and drospirenone 3mg/EE 30mcg/levomefolate Ca 0.451mg (Safyral). One new emergency contraceptive is also available, ulipristal (Ella).

Several OCPs are available on the UF and BCF, and all the miscellaneous contraceptives are currently designated as UF. For the emergency contraceptives, in November 2009, levonorgestrel 0.75 mg (Next Choice, Plan B generic) was designated as BCF and levonorgestrel 1.5 mg (Plan B One Step) was designated as Uniform formulary.

The Contraceptive Drug Class accounted for $87 million in MHS expenditures in FY 2010. In terms of MHS utilization, drospirenone 3mg/EE 20mcg (Yaz, generics) is the most utilized contraceptive, followed by norgestimate 0.18mg/0.215mg/0.25mg/EE 25mcg (Ortho Tri-Cyclen Lo).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended the following conclusions for the contraceptives:

- **Oral Contraceptives Subclass**—For the OCPs subclass, the P&T Committee, voted (15 for, 0 against, 0 abstained, 0 absent) the following conclusions were made:

  1. The differences among the OCPs include estrogen content, progestogen content, regimen, phasic formulation, and non-contraceptive benefits (e.g., acne, premenstrual dysmorphic disorder). The most commonly utilized OCPs are the low-estrogen products containing 20-30 mcg of EE. OCPs commonly include an estrogen with a progestin (combined OCP).
  2. There are no clinically relevant differences in contraceptive effectiveness among the different OCPs, as they all have Pearl Indices (pregnancies per 100 woman-years of use) ranging from < 1 to <3. Current literature does not provide sufficient evidence that combined OCPs containing ≤ 20 mcg EE differ from those with higher EE dosage in preventing pregnancy. However, combined OCPs with ≤ 20 mcg EE are associated with higher rates of changes in bleeding and amenorrhea.
  3. The continuous and extended cycle products (Lybrel, Seasonale, Seasonique, LoSeasonique), allow for shorter, fewer or no periods. The Cochrane reviewers concluded extended or continuous cycle contraceptives are reasonable options for women without contraindications to therapy. Of note, the same regimen can be reproduced by eliminating the pill-free interval of monophasic combined OCPs for 2-3 cycles.
  4. Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, and reduction of acne, dysmenorrhea, endometriosis pain and menstrual migraines, regardless of FDA approval for uses other than pregnancy prevention.
  5. The most commonly reported adverse effects of oral contraceptives include breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.
  6. The use of combined OCPs confers an increased risk of venous thromboembolism (VTE). Based on epidemiological data, the risk of VTE with drospirenone (found in Yaz, drosperinone 3mg/EE 30mcg [Yasmin], Sayfral and Beyaz) is about 2-3 times higher than levonorgestrel-containing OCPs; this risk appears similar to the risk with the third-generation progestins (e.g., desogestrel). FDA is currently reviewing all available data regarding the increased VTE risk with drospirenone-containing oral contraceptives.

7. Comments regarding the newest OCPs include the following: dienogest 2mg/3mg/estradiol valerate 3mg/2mg/2mg/1mg, (Natazia) has complicated dosing instructions if a dose is missed, and the benefits of a quadraphasic OCP remain to be determined. For Beyaz and Safyral, these two products are similar to Yaz and Yasmin, respectively, with the exception of folate, which is added to decrease the risk of neural tube defects if a pregnancy occurs during therapy. Efficacy for both Beyaz and Sayfral was based on data with the innovator products, and clinical trial data is not available. Lo Loestrin Fe has the lowest dose of EE available in an OCP, and had a Pearl Index of 2.92 in the open-label trial used to gain FDA approval. LoSeasonique is a low-EE dose extended cycle OCP given for 91 days (84 days of estrogen and progesterone and 7 days of low dose estrogen).

- **Miscellaneous Contraceptives Subclass**—For the miscellaneous contraceptives subclass, the P&T Committee, based upon its collective professional judgment voted (15 for, 0 against, 0 abstained, 0 absent)

  1. Contraceptive products offer alternative routes of administration including depot medroxyprogesterone acetate (DMPA) injections, a transdermal patch (Ortho Evra), and a vaginal ring (Nuvaring).
  2. Trials have demonstrated similar contraceptive effectiveness for the patch or vaginal ring as the combined OCs. The injectable DMPA contraceptives are highly effective agents; no pregnancy was reported in the three, year-long trials used to gain FDA approval.
  3. Based on a comparative trial, adverse effects of the transdermal patch appear similar to the combined OCP comparator, with the exception of a higher incidence of site application reactions, breast symptoms (e.g., breast tenderness), and dysmenorrhea. Other concerns with the Ortho Evra patch include adhesion problems and application site reactions. The OrthoEvra patch has a black box warning with respect to greater risk of VTE than oral contraceptives, and higher consistent estrogen blood levels (systemic exposure ~ 60% higher than combined OCs).
  4. The most common adverse effects of the vaginal ring were vaginitis, headache, vaginal secretion, weight gain, and nausea. One concern with Nuvaring is deployment limitations related to storage requirements.
  5. Women receiving injectable DMPA may lose significant bone mineral density, an effect which may not be completely reversible. Injectable DMPA products carry a black box warning regarding this risk. Other concerns with injectable DMPA include progressive (and substantial) weight gain, amenorrhea, irregular menses and unpredictable

spotting/bleeding; and lack of immediate reversibility (10 months to return to baseline fertility)

6. The miscellaneous contraceptives serve a niche role and are appropriate contraceptive options for select patients.

- **Emergency Contraceptives Subclass**—For the miscellaneous contraceptives subclass, the P&T Committee, (14 for, 1 against, 0 abstained, 0 absent)

1. Levonorgestrel (Next Choice, generic Plan B; Plan B One Step) has a 3-day window of effectiveness following unprotected intercourse or contraceptive failure, and is available over-the-counter (OTC) for women older than 17 years. Ulipristal (Ella) is a new prescription emergency contraceptive which is effective for up to 5 days after unprotected intercourse.
2. Levonorgestrel 0.75 mg taken in 2 doses 12 hours apart has an efficacy rate of about 95% if taken within 24 hours of unprotected intercourse. Efficacy decreases over time; the efficacy rate is 86% if taken within 25-48 hours, and 58% if taken within 49 to 72 hours of unprotected intercourse. The single-dose 1.5-mg levonorgestrel regimen is as effective as the two-dose regimen taken 12 hours apart.
3. Ulipristal (Ella) is effective at preventing pregnancy following unprotected intercourse, based on the two pivotal trials. No decrease in efficacy occurred over the 120 hour study period. Two head-to-head comparisons of Ella 30 mg with levonorgestrel 1.5mg, are available. In one study Ella was non-inferior to levonorgestrel at preventing pregnancy (Creinin 2006). The other study demonstrated that Ella prevented more unintended pregnancies than levonorgestrel when administered within 72 and 120 hours after unprotected intercourse (observed pregnancy rate with Ella 1.90, 95% CI 1.13-3.12, versus levonorgestrel 2.50, 95% CI 1.68-3.94; p = 0.037; (Glasier 2010).
4. Ella was well tolerated in the clinical trials and its side effect profile is similar to that of levonorgestrel. The most common adverse effects were headache, abdominal pain, nausea and dysmenorrhea. Long term safety with Ella remains unknown.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the oral contraceptive products (OCPs), the miscellaneous contraceptives (patch, vaginal ring, medroxyprogesterone injections), and the emergency contraceptives. CMAs and BIAs were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the OCPs were similar with regard to contraception when used correctly. CMAs were used to analyze the miscellaneous contraceptives. CEAs and CMAs were used to analyze the emergency contraceptives, as efficacy differences between the agents were noted in the clinical

review. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

- CMA and BIA were used to assess the potential impact of cost scenarios where selected OCPs were designated with formulary or NF status on the UF. Two of the selected products are currently designated with BCF status: Yaz, and Yasmin. Four new agents selected are currently designated with formulary status on the UF: Beyaz, Loestrin Fe, LoSeasonique, and Safyral. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.
- CMA alone was performed on the miscellaneous contraceptives (patch, vaginal ring, and medroxyprogesterone intramuscular (IM) and subcutaneous formulations) because there is limited generic competition within the class.
- In the emergency contraceptives subclass, CEA and CMA analyses were used to assess potential impact of pregnancies avoided, based on the clinically reviewed differences between the agents. The relative drug costs of the various treatment regimens were also assessed.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses, the P&T Committee concluded the following:

- **Oral Contraceptives Subclass**—For the OCPs subclass, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 against, 0 abstained, 1 absent) as follows: BIA showed the scenario where all current BCF agents were retained on the BCF, all current UF agents that had been previously reviewed were retained on the UF, and all current NF, as well as the four new agents, were designated with NF status resulted in the lowest cost estimate compared to current MHS expenditures.
- **Miscellaneous Contraceptives Subclass**—For the miscellaneous contraceptives subclass, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 against, 0 abstained, 0 absent) as follows: CMA results showed that the average weighted price per day of therapy at all three points of service for the miscellaneous contraceptives was comparable to formulary agents included in the OCPs subclass.
- **Emergency Contraceptives Subclass**—For the emergency contraceptives subclass, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 against, 0 abstained, 0 absent) as follows: CEA results for the emergency contraceptive agents showed that at current costs, the incremental cost effectiveness ratio with ulipristal (Ella) was less than the projected annual median cost of a live birth in the United States and treatment with ulipristal is a cost-effective alternative compared to levonorgestrel in the MHS. The CMA

results showed that Next Choice was the most cost-effective agent, followed by Plan B One-Step and Ella.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

    - **OCPs Subclass**—For the OCPs subclass, the P&T Committee voted (14 for, 0 against, 0 abstained, 1 absent) that the Jolessa branded generic formulation of levonorgestrel 0.15mg/EE 30mcg, extended regimen (Seasonale, generics) be designated formulary on the UF (UF listing only applies to the Jolessa formulation), and to retain the following drugs on the UF: drospirenone 3mg/EE 20mcg, (Yaz, generics), levonorgestrel 0.1mg/EE 20mcg, (Sronyx, generics), norethindrone1mg/EE 20mcg +/- ferrous fumerate, (Loestin 1/20 or Loestrin Fe 1/20 generics), drospirenone 3mg/EE 30mcg (Yasmim, generics), levonorgestrel 0.15mg/EE 30mcg (Levora, generics), norgestrel 0.3mg/EE 30mcg, (Lo/Ovral, generics), desogestrel 0.15mg/EE 30mcg (Desogen, generics), norethindrone 1.5mg/EE 30mcg +/- ferrous fumerate (Loestrin 1.5/30 or Loestrin Fe 1.5/30, generics), norethindrone 1mg/EE 35mcg (Norinyl 1+35, generics), norgestimate 0.25mg/EE 35mg (Mononessa, generics), norethindrone 0.5mg/EE 35mcg (Modicon, generics), ethynodiol diacetate 1mg/EE 35mcg (Zovia 1/35E, generics), Norinyl 1+50 (norethindrone 1mg/mestranol 50mcg, generics), ethynodiol diacetate 1mg/EE 50mg (Zovia 1/50E), norgestrel 0.5mg/EE 50mcg (Ogestrel), 0.5mg/1mg/EE 35mcg (Necon 10/11 norethindrone), desogestrel 0.15mg/EE 20mcg/10mcg (Mircette, generics), norgestimate 0.18mg/0.215mg/0.25mg/EE 25mcg (Ortho-Tri Cyclen Lo), norgestimate 0.18mg/0.215mg/0.25mg/EE 35mcg (Trinessa generics), levonorgestrel 0.05mg/0.075mg/0.125mg/EE 30mcg/40mcg/30mcg (Trivora, generics), norethindrone 0.5mg/1mg/0.5mg/EE 35mcg (Tri-Norinyl, generics), norethindrone 0.5mg/0.75mg/1mg/EE 35mcg (Ortho-Novum 7/7/7, generics), desogestrel 0.1mg/0.125mg/0.15mg/EE 25mcg (Cyclessa, generics), and Nor-Q-D (norethindrone 0.35mg, (Nor-Q-D generics).

      The following OCPs were designated NF or retained NF status on the UF:

        - norethindrone acetate 1mg/EE 10mcg (Lo Loestrin Fe)
        - levonorgestrel 0.1mg/EE 20mcg + 10mcg (LoSeasonique)
        - drospirenone 3mg/EE 20mcg/levomefolate 0.451mg (Beyaz)

- drospirenone/EE 30mcg/levomefolate 0.451mg (Safyral)
- levonorgestrel 90mcg/EE 20mcg, continuous regimen (Lybrel, generic)
- norethindrone acetate 1mg/EE 20mg, extended regimen (Loestrin 24 Fe)
- norethindrone 0.4mg/EE 35mcg (Ovcon-35 generics; also includes Femcon Fe chewable and Zeosa chewable)
- norethindrone 1mg/EE 50mcg (Ovcon-50)
- levonorgestrel 0.15mg/EE 30mcg + 10mcg, extended regimen (Seasonique, generics)
- norethindrone 1mg/EE 20mcg/30mcg/35mcg/ferrous fumerate 75mg (Estrostep Fe, generics)
- dienogest 2mg/3mg/estradiol valerate 3mg/2mg/2mg/1mg, (Natazia)
- levonorgestrel 0.15mg/EE 30mcg, extended regimen (Seasonale, generics, including Introvale and Quasense), with the exception of Jolessa branded generic

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

- **Miscellaneous Contraceptive Subclass**—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following drugs remain formulary on the UF: norelgestromin/EE 50 mcg transdermal (Ortho Evra), etonorgestrel/EE vaginal ring (NuvaRing), medroxyprogesterone acetate 150 mg/mL (Depo-Provera IM, generics), and medroxyprogesterone acetate 104 mg/0.65 mL (Depo-SubQ Provera 104). No miscellaneous contraceptive agent was recommended for NF placement.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

- **Emergency Contraceptive Subclass**—The P&T Committee recommended (12 for, 0 opposed, 3 abstained, 0 absent) the following drugs remain formulary on the UF: levonorgestrel 0.75mg (Next Choice; Plan B generic), levonorgestrel 1.5mg (Plan B One Step), and that ulipristal (Ella) be designated formulary on the UF. No emergency contraceptive was recommended for NF placement

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following regarding BCF placement for the Contraceptive Agents:

   - **OCPs Subclass**—The P&T Committee recommended (13 for, 1 opposed, 0 abstained, 1 absent) the following drugs remain designated BCF:
     - drospirenone 3mg/EE 20mcg (Yaz, generics)
     - levonorgestrel 0.1mg/EE 20mcg (Sronyx, generics)
     - drosperinone 3mg/EE 30mcg (Yasmin, generics)
     - levonorgestrel 0.15mg/EE 30mcg (Levora, generics)
     - norethindrone 1mg/EE 35mcg (Norinyl 1+35, generics)
     - norgestimate 0.25mg/EE 35mcg (Mononessa, generics)
     - norgestimate 0.18mg/0.215mg/0.25mg/EE 25mcg (Ortho-Tri Cyclen Lo)
     - norgestimate 0.18mg/0.215mg/0.25mg/EE 35mcg (Trinessa, generics)
     - norethindrone 0.35mg (Nor-Q-D, generics).
     - Additionally, levonorgesterol 0.15mg/EE 30 mcg for extended use, the Jolessa branded formulation of Seasonale, was added to the BCF, due to patient compliance and because cost-effective generics are now available at prices comparable to other generic BCF agents.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

- **Miscellaneous Contraceptive Subclass**—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) that none of the miscellaneous contraceptives be designated as BCF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

- **Emergency Contraceptive Subclass**—The P&T Committee recommended (13 for, 0 opposed, 2 abstained, 0 absent) 0.75 mg levonorgestrel (Next Choice; generic Plan B) remain designated BCF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of contraceptive agents, and the conditions for establishing MN for NF medications, the P&T Committee recommended (14 for, 0 against, 0 abstained, 1 absent) MN criteria for the following OCPs: Beyaz, Safyral, Lo Loestrin Fe, and LoSeasonique, and to maintain the existing MN criteria for Seasonale or equivalents (e.g., Quasense, Introvale—excludes Jolessa brand), Loestrin Fe 24 and equivalents, Natazia, Ovcon 50 and equivalents, Lybrel and equivalent, Ovcon 35 and equivalents, including Femcon Fe chewable and Zeosa, Seasonique, and Estrostep Fe and equivalents. (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 against, 0 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the P&T Committee's recommendation, the effective date is January 4, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: EMERGENCY CONTRACEPTION QUANTITY LIMITS (QLs)***—The P&T Committee recommended (13 for, 0 against, 2 abstained, 0 absent) maintaining the current QLs for all the emergency contraceptives of one fill per prescription with no refills.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

Table 1: Drugs in the Contraceptives Class

	Brand Name	Manufacturer	Equiv	Estrogen (mcg)	Progestogen	Estrogen Activity	Progesterone Activity	Androgen Activity
Monophasic OCPs with 10mcg EE	Lo Loestrin Fe	Warner Chilcott	-	EE 10	1.0 mg norethindrone acetate	Low	High	Medium
Monophasic OCPs with 20mcg EE	Aviane	Duramed	AB1	EE 20	0.1 mg levonorgestrel	Low	Low	Low
	Lutera	Watson						
	Orsythia	Qualitest						
	Lessina	Barr	AB2					
	Sronyx	Watson						
	LoSeasonique	Duramed	-	EE 20+ 10	0.10 mg levonorgestrel	Low	Low	Low
	Lybrel	Wyeth	AB	EE 20	0.9 mg levonorgestrel	Low	Low	Low
	Amethyst	Watson						
	Junel 1/20	Barr	AB	EE 20	1.0 mg norethindrone acetate	Low	High	Medium
	Loestrin 1/20	Teva						
	Microgestin 1/20	Watson						
	Junel Fe 1/20	Barr	AB					
	Gildess Fe 1/20	Qualitest						
	Loestrin Fe 1/20	Teva						
	Microgestin Fe 1/20	Watson						
	Loestrin 24 Fe	Warner Chilcott	-	EE 20	1.0 mg norethindrone acetate	Low	High	Medium
	Beyaz	Bayer	-	EE 20	3 mg drospirenone	Low	Unclear	No
	Yaz	Bayer	AB	EE 20	3 mg drospirenone	Low	Unclear	No
	Gianvi	Teva						
	Loryna	Sandoz						
Monophasic OCPs with 25mcg EE	Generess FE	Watson	-	EE 25	0.8 mg norethindrone acetate	Low		
Monophasic OCPs with 30mcg EE	Altavera	Sandoz	AB	EE 30	0.15 mg levonorgestrel	Low	Medium	Medium/High
	Levora 0.15/30-28	Watson						
	Nordette-28	Duramed						
	Portia-28	Barr						
	Seasonale	Duramed	AB					
	Introvale	Sandoz						
	Quasense	Watson						
	Jolessa	Barr						
	Seasonique	Duramed	AB	EE 30 + 10	0.15 mg levonorgestrel	Low	Medium	Medium
	Amethia	Watson						
	Cryselle	Barr	AB	EE 30	0.3 mg norgestrel	Low	Medium	Medium/High
	Lo/Ovral	Wyeth						
	Low-Ogestrel-28	Watson						

	Apri	Barr	AB	EE 30	0.15 mg desogestrel	Low	High	Low
	Desogen	Organon						
	Emoquette	Qualitest						
	Ortho-Cept	Ortho						
	Reclipsen	Watson						
	Solia	Prasco						
	Junel 1.5/30	Barr	AB	EE 30	1.5 mg norethindrone acetate	Low	High	High
	Loestrin 1.5/30	Duramed						
	Microgestin 1.5/30	Watson						
	Gildess Fe 1.5/30	Qualitest	AB					
	Junel Fe 1.5/30	Barr						
	Loestrin-Fe 1.5/30	Duramed/Barr						
	Microgestin Fe 1.5/30	Watson						
	Yasmin	Berlex	AB	EE 30	3 mg drospirenone	Low	Unclear	No
	Ocella	Barr						
	Syeda	Sandoz						
	Zarah	Watson						
	Safyral	Bayer	-	EE 30	3 mg drospirenone	Low	Unclear	No
Monophasic OCPs with 35mcg EE	Brevicon	Watson	AB	EE 35	0.5 mg norethindrone	Medium	Low	Low
	Modicon	Ortho						
	Necon	Watson						
	Nortrel 0.5/35	Barr						
	Femcon Fe (chewable)	Warner-Chilcott	AB	EE 35	0.4 mg norethindrone	Medium	Low	Low
	Zeosa	Teva						
	Ovcon-35	Warner-Chilcott	AB					
	Balziva	Barr						
	Briellyn	Glenmark						
	Zenchent	Watson						
	Mononessa	Watson	AB	EE 35	0.25 mg norgestimate	Medium	Low	Low
	Ortho-Cyclen	Ortho						
	Previfem	Qualitest						
	Sprintec	Barr						

	Cyclafem 1/35	Qualitest	AB	EE 35	1.0 mg norethindrone	Medium	Medium/High	Medium
	Necon	Watson						
	Norinyl 1+35	Watson						
	Nortrel	Barr						
	Ortho-Novum 1/35	Ortho						
	Kelnor	Barr	AB	EE 35	1.0 mg ethynodiol diacetate	Medium	High	Low
	Zovia 1/35E	Watson						
Monophasic OCPs with 50mcg EE or mestranol	Necon 1/50	Watson	AB	Mes 50	1 mg norethindrone	Medium	Medium	Medium
	Norinyl 1+50	Watson						
	Ovcon-50	Warner Chilcott	-	EE 50	1 mg norethindrone	High	Medium	Medium
	Zovia 1/50E	Watson	-	EE 50	1.0 mg ethynodiol diacetate	High	High	Medium/High
	Ogestrel	Watson	-	EE 50	0.5 mg norgestrel	High	High	High
Biphasic OCPs	Necon 10/11	Watson	-	EE 35	0.5 mg/1.0 mg norethindrone	High	Medium	Low/Medium
	Azurette	Watson	AB	EE 20/10mcg	0.150mg desogestrel	Low	High	Low
	Kariva	Barr						
	Mircette	Duramed/Barr						
Triphasic OCPs	Ortho Tri-Cyclen Lo	Ortho	AB	EE 25	0.18/0.215/0.25 mg norgestimate	Low	Low	Low
	Tri-Lo Sprintec	Barr						
	Ortho Tri-Cyclen	Ortho	AB	EE 35	0.18/0.215/0.25 mg norgestimate	Medium	Low	Low
	Trinessa	Watson						
	Tri-Previfem	Qualitest						
	Tri-Sprintec	Barr						
	Enpresse	Barr	AB	EE 30/40/30	0.05/0.075/0.125 mg levonorgestrel	Medium	Low	Low/Medium
	Levonest	Novast Lab						
	Trivora	Watson						
	Aranelle	Barr	AB	EE 35	0.5/1/0.5 mg norethindrone	Medium	Medium	Low/Medium
	Leena	Watson						
	Tri-Norinyl	Watson						
	Cyclafem 7/7/7	Qualitest	AB	EE 35	0.5/0.75/1 mg norethindrone	Medium	Medium	Low/Medium
	Necon 7/7/7	Watson						
	Nortrel 7/7/7	Barr						
	Ortho-Novum 7/7/7	Ortho						

	Caziant	Watson	AB	EE 25	0.1/0.125/0.15 mg desogestrel	Low	High	Low
	Cesia	Prasco						
	Cyclessa	Organon						
	Velivet	Barr						
	Estrostep Fe	Warner-Chilcott	AB	EE 20/30/35	1.0 mg norethindrone	Low	High	Medium
	Tri-Legest FE	Barr						
	Tilia FE	Watson						
Quadriphasic OCPs	Natazia	Bayer	-	Estradiol valerate 3/2/2/1 mg	2/3 mg dienogest	Low		
Progestogen-Only OCPs	Camila	Barr	AB1	-	0.35 mg norethindrone	-		
	Heather	Glenmark						
	Nora-BE	Watson						
	Nor-QD	Watson						
	Errin	Barr	AB2					
	Micronor	Ortho						
	Norethindrone	Glenmark						
	Jolivette	Watson						
Contraceptive patch	Ortho Evra	Ortho	--	*> 50mcg EE (based on Ortho Evra data; ~60% > exposure than with 35 mcg EE)	0.20 mg norelgestromin			
Contraceptive vaginal ring	Nuvaring	Organon		~ 15 mcg EE	~0.12 mg etonogestrel			
Injectable Contraceptives	Depo-subqProvera104**	Pfizer	-	-	104 mg/0.65mL			
	Depo-provera (syr/vl)	Pfizer	AB	-	150 mg/mL			
	Medroxyprogesterone acetate ((syr/vl)	Greenstone						
	Medroxyprogesterone acetate ((syr/vl))	Teva		-	150 mg/mL			
Emergency Contraceptives	Plan B	Duramed	AB	-	0.75 mg levonorgestrel			
	Next Choice	Watson						
	Plan B One-Step	Teva	-	-	1.5mg levonorgestrel			
	Ella	Watson	-	-	30 mg ulipristal			

C. Phosphodiesterase Type 5 (PDE-5) Inhibitors for Erectile Dysfunction (ED)

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the PDE-5 Inhibitors for the treatment of ED. The drugs in the class include sildenafil (Viagra), tadalafil (Cialis), vardenafil oral tablets (Levitra), and one new drug—vardenafil orally dissolving tablets (ODT) (Staxyn). The PDE-5s for ED were previously reviewed in August 2009; at that time, vardenafil was designated with BCF status, with an automated PA requiring a trial of vardenafil prior to sildenafil or tadalafil, which were designated NF. Quantity limits are in place for the PDE-5s for ED.

Vardenafil ODT (Staxyn) contains the same chemical ingredient as vardenafil oral tablets (Levitra). It is available in 10 mg ODT tablets, which is the recommended dose for all patients. In contrast, the starting dose for vardenafil oral tablets is 5 mg in patients older than age 65. Pharmacokinetic studies with vardenafil 10 mg ODT show a higher area under the curve compared to vardenafil 10 mg oral tablets. The two placebo-controlled trials used to obtain FDA approval reported superior efficacy with Staxyn in treating ED. Information regarding the safety, effectiveness, and clinical outcomes of the PDE-5s for ED subclass was considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the PDE-5s for ED:

With regards to efficacy,

1. There are no head-to-head comparative trials between the PDE-5 inhibitors assessing efficacy for ED.
2. Based on meta-analyses by AHRQ, Cochrane, and BioMed Central, indirect comparisons suggest that there are similar improvements between vardenafil oral tablets, sildenafil, and tadalafil in the following endpoints: International Index of Erectile Function (IIEF) "EF" domain change, percentage of patients responding "Yes" to Global Assessment question 1 (which asks "Did this treatment improve your erections?"), and percentage of patients reporting improved erections.
3. The improvement in IIEF score with Staxyn appears similar to that seen in the AHRQ review based on indirect comparison.
4. The 2009 PDE-5 UF review reported there was insufficient evidence to conclude that daily therapy for ED was superior to on demand therapy. There is no new evidence to change this conclusion
5. The improvement in IIIEF score with Staxyn appears similar to that seen in the AHRQ review based on indirect comparison.

With regard to safety,

6. There is insufficient evidence to conclude that there are clinically relevant differences in safety between PDE-5 inhibitors for ED.
7. Clinical trials with vardenafil ODT have identified no safety issues that were not previously identified in the studies of the vardenafil film-coated tablets. However, unlike the other PDE-5s, vardenafil ODT is not recommended for use in patients with renal or hepatic impairment.

With regard to other factors,

8. The PDE-5 inhibitors are highly therapeutically interchangeable, when used for treating ED.

Relative Cost-Effectiveness, Relative Cost-Effectiveness Conclusion, UF Recommendation, BCF Recommendation—Due to contract solicitation issues, the cost effectiveness review and P&T Committee conclusions for the PDE-5 inhibitors for ED will be presented at a future meeting.

1. ***COMMITTEE ACTION: QLs***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) QLs for Staxyn, consistent with the QLs for the other PDE-5 inhibitors for ED. The collective QL for Staxyn is 16 ODT per 90 days in the Mail Order Pharmacy and the collective QL is 6 ODT per 30 days in the Retail Network.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. BCF ISSUES—SIMVASTATIN 80 MG BCF DELETION

In June 2011, the FDA updated the package inserts of products containing simvastatin 80 mg (Zocor, generic; and simvastatin/ezetimibe, Vytorin 80/10) to reflect safety concerns. Based on results of the published SEARCH trial and an internal analysis, the FDA concluded there was a higher risk of myopathy and rhabdomyolysis with simvastatin 80 mg, when compared to simvastatin 20 mg. Accordingly, there are new contraindications with other drugs and warnings limiting use to patients already stabilized on simvastatin 80 mg for longer than 12 months. Currently there over 11,000 MHS patients receiving simvastatin 80 mg. Although there are several limitations to this data, including the fact the FDA did not evaluate patient-level adverse reaction reports, the P&T Committee agreed to remove simvastatin 80 mg from the BCF, and to update the existing automated step therapy criteria for the Antilipidemic-1s.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (12 for, 1 opposed, 1 abstained, 1 absent) to remove the simvastatin 80 mg dosage strength (Zocor; generics) from the BCF.

Director, TMA, Decision: ☒Approved □ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. Montelukast (Singulair)—PA: PA criteria were proposed for montelukast. National and international treatment guidelines, as well as pertinent published clinical literature, were used to define supportable indications for use of montelukast. Utilization data from the MHS population was presented to the P&T Committee with respect to indications deemed supportable.

1. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (12 for, 1 opposed, 1 abstained, 1 absent) the following PA criteria should apply to montelukast. Montelukast will be approved only for patients under the age of 19 and patients 19 or older who show evidence of use for an FDA-approved and guideline-supported indication. All current and new users of montelukast must meet one of the following criteria to pass through the PA process.

    a) Automated PA criteria:

        (1) Patient is ≤18 years of age.

        (2) Patient has received an inhaled corticosteroid or combination inhaled corticosteroid/inhaled long-acting beta agonist during the previous 180 days at a MTF, retail network pharmacy, or the mail order pharmacy.

    b) Manual PA criteria:

        (1) Coverage approved if:

            (a) The patient/provider documents use of montelukast for seasonal allergic rhinitis (or nasal polyposis) with evidence of a inadequate therapy with a nasal corticosteroid dispensed during the previous 180 days at a MTF, a retail network pharmacy, or the mail order pharmacy; or

(b) The patient/provider documents intolerance (due to experienced adverse events) or contraindication to either inhaled or intranasal corticosteroids.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: Montelukast PA IMPLEMENTATION PERIOD***— The P&T Committee recommended (12 for, 0 opposed, 2 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision. The effective date is February 1, 2012.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Prescription Omega-3 Acid (Lovaza)—PA: Prior authorization for all current and new users of prescription omega-3-acid (Lovaza) was recommended at the February 2011 Committee meeting, limiting Lovaza use to the current FDA-approved indication for patients with triglyceride (TG) levels greater than 500 mg/dL. Since implementation of the PA requirements in July 2011, several questions regarding the PA form have been raised by providers and patients regarding patients with TG levels less than 500 mg/dL. P&T Committee members were briefed on the current status of the Lovaza PA program. Recommendations were made to clarify the decision point for patients with TG < 500mg/dL to more accurately reflect the intent of the P&T Committee.

1. ***COMMITTEE ACTION: LOVAZA PA FORM CLARIFICATION AND IMPLEMENTATION***—The P&T Committee recommended (12 for, 0 against, 1 abstained, 2 absent) updating the Lovaza PA form as noted above. Implementation can occur administratively.

Director, TMA, Decision: ☑ Approved □ Disapproved

Approved, but modified as follows:

VII. ITEMS FOR INFORMATION

A. Pharmacy Outcomes Research Team (PORT): The PORT updated the P&T Committee on prescribing trends and patient outcomes in several drug classes where step therapy (automated PA) had been implemented.

B. Rosiglitazone (Avandia) Risk Evaluation and Mitigation Strategy (REMS)—Rosiglitazone (Avandia) was designated NF at the November 2010 P&T Committee meeting, due to well-established safety concerns and the FDA requirement for a REMS program by the manufacturer. The details of the REMS are now available. Rosiglitazone products will be withdrawn from supply chains beginning October 18, 2011, and patients will not be able to buy their prescriptions in retail pharmacies after November 18, 2011. Further information regarding availability will be provided on the TRICARE Formulary Search Tool.

C. Saxagliptin/Metformin ER (Kombiglyze XR) PA Criteria—The manual PA criteria for Kombiglyze XR were updated to remove the criteria regarding adverse events or history of lactic acidosis with metformin.

D. Disease-Modifying Drugs for Multiple Sclerosis Drug Class—The UF review of the injectable drugs for multiple sclerosis originally scheduled for this meeting was tabled.

VIII. ADJOURNMENT

The meeting adjourned at 1700 hours on August 10, 2011, and at 1130 hours on August 11, 2011. The next meeting will be in November 2011.

Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix C—Table of Implementation Status of UF Recommendations/Decisions

Appendix D—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

27 Oct 2011
(Date)

Appendix A—Attendance

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CDR Joe Lawrence	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Pete Bulatao, MSC for COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
CAPT Edward Norton	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
COL Ted Cieslak, MC	Army, Physician at Large
Major Jeremy King, MC	Air Force, OB/GYN Physician
LTC Bruce Lovins, MC	Army, Family Practice Physician
CDR Michelle Perello for CAPT Walter Downs, MC	Navy, Internal Medicine Physician
LT Christina Olsen for CDR Eileen Hoke, MC	Navy, Pediatrics
Lt Col Sam Munro, MC	Air Force, Physician at Large
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
CDR Michele Hupp, MSC	Defense Medical Standardization Board
Maj Achilles Hamilothoris	Defense Logistics Agency Troop Support
Guests	
CDR Joe Bryant	Indian Health Service
Dr. Lisa Longo	VA PBM
ENS Nicole Crosby	DoD Pharmaceutical Operations Directorate
Debra Nguyen	UIW Pharmacy Intern

Appendix A—Attendance (continued)

Others Present	
Lt Col Rey Morales	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
MAJ Misty Cowan	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Dr. Bradley Clarkson	Pharmacy Resident

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Drospirenone 3 mg/EE 20 mcg / levomefolate 0.451 mg (Beyaz) **Contraceptives**	• Use of ALL formulary oral contraceptives is contraindicated (e.g., due to hypersensitivity), and treatment with Beyaz is not contraindicated.
Drospirenone 3 mg/EE 30 mcg / levomefolate 0.451 mg (Sayfral) **Contraceptives**	• Use of ALL formulary oral contraceptives is contraindicated (e.g., due to hypersensitivity), and treatment with Sayfral is not contraindicated.
Norethindrone acetate 1mg/EE 10 mcg / ferrous fumarate 75 mg (Lo Loestrin Fe) **Contraceptives**	• Use of ALL formulary oral contraceptives is contraindicated (e.g., due to hypersensitivity), and treatment with Lo Loestrin Fe is not contraindicated.
Levonorgestrel 0.1 mg/EE 20 mcg, EE 10 mcg for extended use (LoSeasonique) **Contraceptives**	• Use of ALL formulary oral contraceptives is contraindicated (e.g., due to hypersensitivity), and treatment with Lo Seasonique is not contraindicated.
Estradiol valerate/dienogest (Natazia) **Contraceptives**	(No change from previous criteria) • Use of formulary agents contraindicated. • No alternative formulary agent available (if other oral contraceptive agents do not provide adequate bleeding and cycle control).
Norethindrone acetate 1mg/EE 20 mcg (Loestrin 24 Fe) **Contraceptives**	(No change from previous criteria) • Use of formulary agents contraindicated.
Levonorgestrel 0.9 mg /EE 20 mcg for extended use (Lybrel and equivalents) **Contraceptives**	No change from previous criteria) • The patient has experienced significant adverse effects from formulary combined Ocs and is expected to tolerate a non-formulary contraceptive agent. • Use of formulary combined Ocs has resulted in therapeutic failure.

Drug / Drug Class	Medical Necessity Criteria
Norethindrone 0.4mg/EE 35 mcg (Ovcon-35 and equivalents; includes Femcon Fe chewable and Zeosa) Norethindrone 1mg/EE 50mcg (Ovcon-50) Levonorgestrel 0.15 mg /EE 30 mcg, EE 10 mcg for extended use (Seasonique) Norethindrone 1 mg/EE 20/30/35 mcg / ferrous fumerate 75mg (Estrostep Fe and equivalents) Levonorgestrel 0.15 mg/EE 30 mcg for extended use (Seasonale and equivalents; with the exception of Jolessa brand) **Contraceptives**	(No change from previous criteria) • Use of formulary agents contraindicated. • The patient has experienced significant adverse effects from formulary combined Ocs and is expected to tolerate a non-formulary contraceptive agent. • Use of formulary combined Ocs has resulted in therapeutic failure.
Bromocriptine mesylate (Cycloset) **Non-Insulin Diabetes Drugs – Dopamine Agonists**	• The use of formulary alternatives is contraindicated. • The patient has experienced significant adverse effects from the formulary alternatives.
Diclofenac potassium liquid filled capsules (Zipsor) Diclofenac potassium powder packets (Cambia) Naproxen sodium ER (Naprelan CR) Mefenamic acid (Ponstel) **Oral Non-steroidal Anti-Inflammatory Drugs (NSAIDs)**	• Use of formulary alternatives is contraindicated.

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2011	**Contraceptive Agents** **Oral Contraceptives Subclass**	UF Review	▪ EE 20 mcg; 3 mg drospirenone (Yaz) ▪ EE 20 mcg; 0.1 mg levonorgestrel (Lutera, Sronyx or equiv) ▪ EE 30 mcg; 3 mg drospirenone (Yasmin) ▪ EE 30 mcg; 0.15 mg levonorgestrel (Levora, Nordette or equiv) ▪ EE 30 mcg; 0.15 mg levonorgestrel extended cycle (**Jolessa only**) ▪ EE 35 mcg; 1.0 mg norethindrone (Norinyl 1+35, Ortho Novum 1/35 or equiv) ▪ EE 35 mcg; 0.25 mg norgestimate (Mononessa, Ortho Cyclen or equiv) ▪ EE 25 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg; 0.18/0.215/0.25 mg norgestimate (Trinessa, Ortho Tri-Cyclen or equiv) ▪ 0.35 mg norethindrone (Nor-QD, Micronor or equiv)	▪ EE 20 mcg; 1.0 mg norethindrone ▪ EE 20 mcg; 1.0 mg norethindrone; ferrous fumarate ▪ EE 30 mcg; 0.3 mg norgestrel ▪ EE 30 mcg; 0.15 mg desogestrel ▪ EE 30 mcg; 1.5 mg norethindrone ▪ EE 30 mcg; 1.5 mg norethindrone; ferrous fumarate ▪ EE 35 mcg; 0.5 mg norethindrone ▪ EE 35 mcg; 1.0 mg ethynodiol diacetate ▪ Mestranol 50 mcg; 1 mg norethindrone ▪ EE 50 mcg; 1 mg ethynodiol diacetate ▪ EE 50 mcg; 0.5 mg norgestrel ▪ EE 35 mcg; 0.5/1.0 mg norethindrone ▪ EE 20/10 mcg; 0.15 mg desogestrel ▪ EE 30/40/30 mcg; 0.05/0.075/0.125 mg levonorgestrel ▪ EE 35 mcg; 0.5/1/0.5 mg norethindrone ▪ EE 35 mcg; 0.5/0.75/1 mg norethindrone ▪ EE 25 mcg; 0.1/0.125/0.15 mg desogestrel	▪ EE 10 mcg; 1.0 mg norethindrone; ferrous fumarate (Lo Loestrin Fe) ▪ EE 20 mcg/norethindrone acetate 1 mg – 24 day regimen (Loestrin 24 Fe) ▪ EE 20 mcg; 3 mg drospirenone; levomefolate calcium 0.451mg (Beyaz) ▪ EE 20 mcg/levonorgestrel 0.9 mg – 28 day continuous regimen (Lybrel or equiv) ▪ EE 20/10 mcg; 0.10 mg levonorgestrel (LoSeasonique or equiv) ▪ EE 30 mcg; 3 mg drospirenone; levomefolate calcium 0.451mg (Safyral) ▪ EE 30 mcg; levonorgestrel 0.15 mg generics (Seasonale or equiv – excludes Jolessa) ▪ EE 35 mcg; 0.4 mg norethindrone (Femcon Fe chew tab, Ovcon 35 or equiv) ▪ EE 50 mcg; 1 mg norethindrone (Ovcon 50) ▪ EE 30/10 mcg; 0.15 mg levonorgestrel (Seasonique or equiv) ▪ EE 20/30/35 mcg; norethindrone 1 mg (Estrostep Fe or equiv) ▪ Estradiol valerate 3/2/2/1 mg; dienogest 2/3 mg (Natazia)	Pending signing of minutes/ 60 days	-	-

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2011	**Contraceptive Agents** **Miscellaneous Contraceptives and Emergency Contraceptives Subclass**	UF Review	*Miscellaneous Contraceptives* (None) *Emergency Contraceptives* ▪ 0.75 mg levonorgestrel (Next Choice; generic Plan B)	*Miscellaneous Contraceptives* ▪ norelgestromin 0.2 mg transdermal (Ortho-Evra) ▪ etonorgestrel 0.12 mg vaginal ring (Nuvaring) ▪ 104 mg/0.65mL depot medroxyprogesterone acetate injection (Depo-subq Provera 104) ▪ 150 mg/mL depot medroxyprogesterone acetate injection *Emergency Contraceptives* ▪ 1.5 mg levonorgestrel (Plan B One Step) ▪ 30 mg Ulipristal acetate (Ella)	▪ No miscellaneous or emergency contraceptives designated NF	Pending signing of minutes/ 60 days	Emergency Contraceptives: 1 fill per prescription/no refills	-
Aug 2011	**Non-Steroidal Anti-inflammatory Drugs**	UF Review	▪ ibuprofen 400 mg, 600 mg & 800 mg, & ~~125 mg/5 mL susp~~ (generic) ▪ indomethacin 25 mg & 50 mg (generic) ▪ meloxicam 7.5 mg & 15 mg (generic) ▪ naproxen 250 mg & 500 mg (generic)	▪ celecoxib (Celebrex) ▪ diclofenac/misoprostol (Arthrotec) ▪ diclofenac potassium tablets (Cataflam generic) ▪ diclofenac sodium tablets (Voltaren generic) ▪ diflunisal ▪ etodolac ▪ fenoprofen ▪ flurbiprofen ▪ ketoprofen ▪ ketorolac ▪ meclofenamate ▪ nabumetone ▪ naproxen sodium 275 mg & 550 mg (Anaprox, generic) ▪ oxaprozin ▪ piroxicam ▪ sulindac ▪ tolmetin ▪ naproxen/esomeprazole (Vimovo)	▪ diclofenac potassium liquid filled capsules (Zipsor) 25 mg ▪ diclofenac potassium powder packets 50 mg (Cambia) ▪ naproxen sodium ER (Naprelan CR, generic) 375 mg, 500 mg, & 750 mg ER tabs, dosing card ▪ mefenamic acid (Ponstel, generic) 250 mg	Pending signing of minutes/ 60 days	None	-

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2011	**Renin-Angiotensin Antihypertensive class** **Subclass: ARBs**	New Drugs in Already Reviewed Class Azilsartan (Edarbi) Aliskiren /amlodipine /HCTZ (Amturnide)	No change from previous decision Aug 2010 **ACE Inhibitors** ▪ Lisinopril (Prinvil, Zestril, generic) ▪ lisinopril HCT (Prinzide, Zestoretic generic) ▪ Captopril (Capoten, generic) ▪ Ramipril (Altace, generic) **ACE-Inhibitor/CCB** ▪ Benazepril/amlodipine (Lotrel, generic) **ARBs** ▪ Losartan (Cozaar, generic) ▪ Losartan/HCTZ (Hyzaar, generic) ▪ Telmisartan (Micardis) ▪ Telmisartan/HCTZ (Micardis HCT) ▪ Valsartan (Diovan) Valsartan/HCTZ (Diovan HCT)	*August 2011* • Azilsartan (Edarbi) • Aliskerin/amlodipine/HCTZ (Amturnide) See August 2010 minutes for previous decision	▪ No change from previous decision Aug 2010. Not applicable (no drug designated non-formulary)	Pending signing of minutes/ 60 days	Step therapy (automated PA)	Step therapy (automated PA) with the following as the step-preferred drugs: ▪ losartan ±HCTZ ▪ telmisartan ±HCTZ ▪ telmisartan/ amlodipine ▪ valsartan ±HCTZ ▪ valsartan/ amlodipine ▪ valsartan/ amlodipine/HCTZ Note: Azilsartan (Edarbi) and Aliskiren/ /amlodipine/HCTZ (Amturnide) are UF but behind the step
Aug 2011	**Non-Insulin Diabetes Drugs** **Subclass: Dopamine agonists**	New Drug in Already Reviewed Class Bromocriptine mesylate (Cycloset)	No change from previous decision Nov 2010 **Biguanides** ▪ Metformin IR 500, 850, 1000 mg (generics) ▪ Metformin ER 500, 750 mg (generics) **Sulfonylureas** ▪ Glipizide (generics) ▪ Glyburide (generics) ▪ Glyburide micronized (generic)	See November 2010 minutes for other subclasses	*August 2011* ▪ Bromocriptine mesylate (Cycloset) ▪ See November 2010 minutes for other subclasses (no change to previous decision)	Pending signing of minutes/ 60 days	Step therapy (Automated PA)	Step Therapy (automated PA) with metformin and sulfonylureas as step-preferred drugs

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 201	**Narcotic Analgesics** **Subclass: Low potency single analgesic agents**	New Drug in Already Reviewed Class Buprenorphine 47hosphodies (Butrans)	**Low potency single analgesic agents (Nov 2009)** ▪ Tramadol IR	**Low potency single analgesic agents:** *August 2011* • Buprenorphine Transdermal (Butrans) *Feb 2007 & Nov 2009* • Buprenorphine sublingual • Butorphanol intranasal • Pentazocine/naloxone • Nalbuphine • Tramadol (Rybix)	▪ Tramadol ER (Ultram ER, Ryzolt – Nov 2009)	Pending signing of minutes/ 60 days	PA: Manual QL – 4 per month	Manual PA for buprenorphine transdermal system (Butrans) to ensure safe and appropriate use

Appendix D—Table of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
BCF	Basic Core Formulary
BIA	budget impact analysis
CV	cardiovascular
CEA	cost-effectiveness analysis
CCB	calcium channel blocker
CFR	Code of Federal Regulations
CMA	cost minimization analysis
COX-2	cyclooxygenase-2
DA	dopamine agonist
DERP	Oregon Drug Effectiveness Review Project
DHP	dihydropyridine
DoD	Department of Defense
DPP-4	dipeptidyl-peptidase-4
DRI	direct renin inhibitor
ED	erectile dysfunction
EE	ethinyl estradiol
ER	extended release
FDA	U.S. Food and Drug Administration
FDC	fixed dose combination
GI	gastrointestinal
HbA1C	Hemoglobin A1C
HCTZ	hydrochlorothiazide
IIED	International Index of Erectile Function
IM	intramuscular
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NF	nonformulary
NSAIDs	Non-steroidal Anti-inflammatory Drug Class
OCPs	oral contraceptive products
ODT	orally dissolving tablets
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PDE-5	48hosphodiesterase type-5
PORT	Pharmaceutical Outcomes Research Team
PPI	proton pump inhibitor
QL	quantity limit
RAAs	Renin Angiotensin Antihypertensives
Sus	sulfonylureas
TZDs	thiazolidinediones
T2DM	Type 2 Diabetes Mellitus
UF	Uniform Formulary
VTE	venous thromboembolism

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2011

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 11 and 12, 2011, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May Minutes**—Jonathon Woodson M.D. Director, approved the minutes for the February 2011 DoD P&T Committee meeting on May 9, 2011.

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Non-Insulin Diabetes Drugs: Dipeptidyl Peptidase-4 Inhibitor (DPP-4)/Biguanide Fixed-Dose Combination (FDC)—Saxagliptin/Metformin XR (Kombiglyze XR)

Relative Clinical Effectiveness—Kombiglyze XR is a FDC product containing the DPP-4 inhibitor saxagliptin (Onglyza) and the biguanide metformin extended-release (ER) (generic Glucophage XR) in one tablet. This drug is the second FDA-approved DPP-4/metformin FDC product. The Non-Insulin Diabetes drug class, which included the DPP-4s and biguanides separately, as well as combinations, was reviewed during the November 2010 P&T Committee meeting. The clinical evaluation for Kombiglyze XR included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Kombiglyze XR is approved for use as adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. In November 2010, sitagliptin (Januvia) and sitagliptin/metformin immediate-release (IR) (Janumet) were designated with Basic Core Formulary (BCF) status and saxagliptin was designated with Uniform Formulary (UF) status. Automated Prior Authorization or Step Therapy applies to the DPP-4 subclass, which requires a trial of metformin alone or a sulfonylurea (SU) prior to use of sitagliptin, sitagliptin/metformin IR, or saxagliptin. The generic metformin ER component of Kombiglyze XR is available on the BCF as a single agent.

Clinical trials with sitagliptin and saxagliptin when used as monotherapy show reduction in hemoglobin A1C (HbA1C) of 0.4 - 0.79%. The saxagliptin/metformin FDC provides a 2.5% decrease in HbA1c from baseline. There are no head-to-head trials comparing saxagliptin/metformin ER (Kombiglyze XR) and sitagliptin/metformin IR (Janumet). However, in a head-to-head non-inferiority trial, sitagliptin/metformin IR lowered HbA1c by approximately 0.1% more from baseline than saxagliptin/metformin IR. Saxagliptin was considered non-inferior to sitagliptin. While statistical significance was achieved, the difference between the two agents is not clinically significant. There are no clinically relevant differences between sitagliptin and saxagliptin when combined with metformin in terms of glycemic control, and changes in lipid profile, weight, or blood pressure.

The product labeling for Kombiglyze XR contains the same contraindications and warnings as metformin. Renal and hepatic impairment remains a concern as well as other conditions that increase the risk of developing lactic acidosis. Kombiglyze XR can be dosed once daily. To achieve the target dose of metformin, patients can take an additional dose of metformin or take two 2.5mg/1000mg Kombiglyze XR tablets together once daily.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) saxagliptin/metformin XR (Kombiglyze XR) offers no clinically meaningful therapeutic advantage over sitagliptin/metformin IR (Januvia) in terms of efficacy, safety, or tolerability.

Relative Cost-Effectiveness—Cost-minimization analysis (CMA) was performed to evaluate the cost of saxagliptin/metformin ER (Kombiglyze XR) in relation to the other UF DPP-4 inhibitor/biguanide FDC agent, sitagliptin/metformin IR (Janumet), and to generic metformin IR or ER in combination with sitagliptan (Januvia) or saxagliptan (Onglyza). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that saxagliptin/metformin ER (Kombiglyze XR) tablets were more costly, compared with the other DPP-4s currently designated with BCF or UF status.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 0 absent) saxagliptin/metformin ER (Kombiglyze

XR) remain formulary on the UF. Prior authorization/step therapy for the DPP-4s would require a trial of metformin or sulfonylurea prior to use of Kombiglyze XR for new patients.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 0 absent) saxagliptin/metformin ER (Kombiglyze XR) be excluded from the BCF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to Kombiglyze XR. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for metformin or sulfonylurea at any Military Health Service (MHS) pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order) during the previous 180 days. OR

      (2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, or Onglyza) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria, if automated criteria are not met:

(1) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is October 5, 2011

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

B. Ophthalmic-1 Class—Bromfenac 0.09% Ophthalmic Solution (Bromday)

Relative Clinical Effectiveness—Bromfenac 0.09% ophthalmic solution (Bromday) is a non-steroidal anti-inflammatory drug (NSAID). It is the only ophthalmic NSAID approved for once daily dosing. Bromday is the same formulation of bromfenac (Xibrom) that was previously a twice daily dosed product. The branded formulation Xibrom was withdrawn from the market in February 2011 by the manufacturer. At the time of the May 2011 P&T Committee meeting, no generic formulations of Xibrom were approved. The Ophthalmic-1 Class was reviewed at the August 2010 P&T Committee meeting. All the ophthalmic NSAIDs are designated with formulary status on the UF; none are designated with BCF status. The clinical evaluation included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Bromday was approved under a Supplemental New Drug Application using the data from Xibrom to change the dosing regimen to once daily dosing. Two Phase III placebo-controlled studies concluded that bromfenac dosed once daily for 16

days is effective for treating inflammation and pain in patients who have undergone cataract extraction with intraocular lens implantation. There are no head-to-head clinical trials comparing the bromfenac once-a-day formulation with the twice-a-day formulation. There are no studies comparing the bromfenac once daily formulation with any other ophthalmic NSAIDs. The safety profile of bromfenac is consistent with the other ophthalmic NSAIDs. The most common adverse events in the Phase III clinical trials that led to drug discontinuation and which occurred in a higher incidence than placebo were eye inflammation, photophobia, and eye pain. Based on the safety data from two Phase III studies, there are no clinically relevant differences between bromfenac ophthalmic solution and other ophthalmic NSAIDs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) there is no published evidence to suggest that bromfenac ophthalmic solution 0.09% (Bromday) has a compelling clinical advantage over other ophthalmic NSAID products currently included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of bromfenac 0.09% ophthalmic solution (Bromday) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other Ophthalmic-1 NSAIDs prescribed for postoperative pain and inflammation following cataract surgery. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Bromday compared to other UF agents. CMA results showed the projected weighted average cost per day for Bromday is higher than generic ophthalmic NSAIDs, but comparable in price to brand name ophthalmic NSAIDs.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) bromfenac 0.09% ophthalmic solution (Bromday) is cost-effective relative to the other branded Ophthalmic-1 NSAIDs in this class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 1 absent) bromfenac 0.09% ophthalmic solution (Bromday) remain formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 1 absent) bromfenac 0.09% ophthalmic solution (Bromday) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Alpha Blockers for Benign Prostatic Hyperplasia (BPH)—Tamsulosin/Dutasteride (Jalyn)

Relative Clinical Effectiveness—Tamsulosin/dutasteride (Jalyn) is a FDC product containing tamsulosin (Flomax, generics), an uroselective alpha-1 blocker (A1B) and dutasteride (Avodart), a 5-alpha reductase inhibitor (5-ARI). Jalyn is the first combination product for BPH. The drug is indicated for treatment of symptomatic BPH in men who have an enlarged prostate (>30 mL prostate volume). Jalyn is classified in the A1B subclass of the BPH agents, which was last reviewed in May 2010. Automated PA/Step Therapy applies to the A1B subclass, which requires a trial of generic tamsulosin or alfuzosin (Uroxatral) for new patients. For the 5-ARI subclass, finasteride (Proscar, generics) is designated with BCF status, and dutasteride (Avodart) is nonformulary on the UF. The clinical evaluation for Jalyn included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

FDA approval for Jalyn is based on the large randomized controlled four-year study, Combination of Avodart and Tamsulosin (CombAT), which evaluated the combination versus individual components. Results from the CombAT study showed the combination of dutasteride and tamsulosin (Jalyn) was not superior to dutasteride monotherapy for males with BPH with an enlarged prostate (>30ml), in terms of objective clinical progression to acute urinary retention (AUR) or BPH-related surgery.

The combination was superior to both tamsulosin and dutasteride monotherapy in terms of improvement of BPH-related symptoms.

The safety and tolerability data from the ComBAT study did not show a clinically relevant difference with Jalyn as compared to monotherapy with tamsulosin or dutasteride. There was a numerical increase in the incidence of cardiac failure with combination tamsulosin/dutasteride, however the FDA determined that co-morbidities were more likely the cause than the drug effect. There was a higher incidence of sexual adverse events (e.g., erectile dysfunction, retrograde ejaculation) with Jalyn, but these did not lead to a higher discontinuation rate with Jalyn, compared to the single agents administered as monotherapy.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that the FDC tamsulosin/dutasteride (Jalyn) is superior to tamsulosin and dutasteride monotherapy in terms of delaying BPH symptoms. However, it was not superior to dutasteride in delaying clinical progression to AUR and BPH-related surgery. There were no clinically relevant differences for Jalyn as compared to tamsulosin or dutasteride monotherapy in terms of safety and tolerability. The P&T Committee also agreed there is a high degree of therapeutic interchangeability between Jalyn and other combinations of selective A1B and a 5-ARI (e.g., tamsulosin/finasteride).

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of tamsulosin/dutasteride (Jalyn) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other uroselective A1Bs and 5-ARIs used for BPH. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Jalyn compared to other UF agents. Results from the CMA showed the projected weighted average cost per day for Jalyn was higher than the most cost-effective combination—generic tamsulosin and generic finasteride. However, Jalyn was more cost-effective than its individual components taken separately.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the combination of tamsulosin and finasteride administered together represents the most cost-effective combination of uroselective A1Bs and 5-ARIs for treatment of BPH. The FDC tamsulosin/dutasteride (Jalyn) is a cost-effective alternative relative to other combinations of A1Bs and dutasteride (Avodart).

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 1 opposed, 1 abstained, 1 absent) tamsulosin/dutasteride (Jalyn) remain formulary on the UF, with automated PA/Step Therapy requiring generic tamsulosin or alfuzosin (Uroxatral) for new patients.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 1 absent) tamsulosin/dutasteride (Jalyn) be excluded from the BCF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—Prior authorization for the A1Bs requires a trial of a step-preferred drug [tamsulosin or alfuzosin (Uroxatral)] prior to a non-step-preferred A1B [silodosin (Rapaflo)]. Tamsulosin/dutasteride (Jalyn) would be designated non-step-preferred. The P&T Committee recommended (13 for, 1 opposed, 2 abstained, 1 absent) the following PA criteria apply to tamsulosin/dutasteride (Jalyn):

    a) Automated PA criteria:
        (1) The patient has received a prescription for a preferred agent in the A1B subclass at any MHS pharmacy point of service (MTFs, retail network pharmacies, or home delivery) during the previous 180 days.

b) Manual (paper) PA criteria, if automated criteria are not met:

(1) The patient has received a trial of tamsulosin or alfuzosin and had an inadequate response and requires therapy with both an A1B and 5-ARI.
(2) The patient has received a trial of alfuzosin but was unable to tolerate it due to adverse effects but is expected to tolerate tamsulosin and requires therapy with both an A1B and 5-ARI.
(3) Treatment with alfuzosin is contraindicated for this patient (e.g., due to hypersensitivity) but tamsulosin is not contraindicated, and the patient requires therapy with both an A1B and 5-ARI.
(4) The patient requires therapy with both an A1B and 5-ARI and requires a fixed-dose combination (e.g., swallowing difficulties).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 2 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the P&T Committee's recommendation, the effective date is October 5, 2011.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UF DRUG CLASS REVIEWS

A. Atypical Antipsychotic Drugs

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the drugs in the atypical antipsychotics (AAP) Drug Class. The clinical review for the oral AAP drugs included, but was not limited to,

sources of information listed in 32 CFR 199.21(e)(1). The injectable AAPs were not included in the review.

The class is comprised of the following agents: clozapine (Clozaril, generics; Fazaclo), risperidone (Risperdal, Risperdal orally disintegrating tablet (ODT), generics), aripiprazole (Abilify, Abilify Discmelt), asenapine (Saphris), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine IR and ER (Seroquel; Seroquel XR), and ziprasidone (Geodon).

The AAP Drug Class has not previously been reviewed for UF status, although quetiapine IR (Seroquel) and risperidone tablets were added to the BCF in May 2003 (prior to implementation of the Uniform Formulary Rule). Clarifications were made in August 2007 to include quetiapine ER (Seroquel XR) on the BCF and to exclude risperidone ODT. Currently, risperidone is the only AAP drug available in a generic formulation. The anticipated generic entries in the class are Zyprexa, Geodon, Abilify, and Seroquel IR, with patents set to expire in 2011 to 2014.

The AAP Drug Class is associated with a significant cost within the MHS; expenditures exceed $200 million annually. In terms of MHS utilization, quetiapine is the most utilized AAP, followed by generic risperidone. Aripiprazole is the third most utilized agent but accounts for most of the expenditures in the class.

The Pharmacy Outcomes Research Team (PORT) analyzed utilization and prescribing patterns in the MHS and noted that approximately 60% of AAP use in the MHS appears to be consistent with FDA-approved labeling. This estimate is higher than noted in the literature and may be overstated. The most common diagnosis codes for the AAPs differed by the population studied. For the active duty population, depression was the most commonly reported diagnosis code (53%, although it is unclear whether AAP use was for insomnia or to augment antidepressant effect). In the non-active duty population (ages 18–64 years), depression was the most commonly reported diagnosis code (61%). In contrast, attention deficit hyperactivity was the most commonly reported diagnosis code in the pediatric population (62%), compared with the over-65 population, where dementia was the most common diagnosis code (52%).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) the following conclusions for the AAPs:

1. Schizophrenia: All AAPs are efficacious in treating schizophrenia. Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial suggests that olanzapine is superior to the other AAPs in efficacy, but use is limited by adverse events. The four newest AAPs (asenapine, iloperidone, lurasidone, and paliperidone) are superior to placebo in treating schizophrenia, but the data is limited to small trials of short duration.

2. Bipolar Disorders: AAPs are used as adjunctive therapy to mood stabilizers in treating mania and mixed episodes. Six AAPs are FDA-approved for use in bipolar disorders (aripiprazole, asenapine, olanzapine, quetiapine, ziprasidone, and risperidone). Recommendations from the 2010 VA/DoD Clinical Practice Guideline (CPG) for bipolar disorder conclude olanzapine and quetiapine have more positive evidence than the other AAPs.
3. Major Depressive Disorder (MDD): For treatment-resistant MDD, AAPs are superior to placebo in augmenting antidepressant therapy. Three AAPs are FDA-approved for the treatment of MDD: aripiprazole, olanzapine/fluoxetine, and quetiapine ER. Data from systematic reviews suggests more positive evidence exists with quetiapine and aripiprazole for this indication. Risperidone also shows benefit in treating MDD, but is not FDA-approved.
4. Post-Traumatic Stress Disorder (PTSD): The available evidence from the 2010 VA/DoD CPG for PTSD and the American Psychiatric Association supports some benefit for the AAPs when used as adjunctive therapy to cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs). The results of one meta-analysis show olanzapine and risperidone were more efficacious than placebo. None of the AAPs are FDA-approved for treating PTSD.
5. Dementia: There is evidence from systematic reviews that dementia symptoms of aggression and agitation are improved with AAPs (risperidone and olanzapine) but there is no benefit conferred in terms of cognition and functionality. Use of AAPs for psychiatric symptoms and behavioral disturbances in dementia patients is not approved by the FDA and is associated with significant risks of adverse events, including development of heart failure, cerebrovascular accident, and sudden cardiac death.
6. Insomnia: None of the AAPs are FDA-approved for treating insomnia. USCENTCOM MOD-10, military guidance for deployment, currently allows for the use of low-dose quetiapine (25 mg) for sleep with no waivers required. In the absence of other psychiatric comorbidities, the use of low-dose AAPs for primary insomnia should be discouraged due to the lack of supportive evidence, risk of adverse events (metabolic and cardiac), and lack of monitoring (e.g., EKG) for adverse events in-theatre. Other drug options to treat insomnia are available on the CENTCOM formulary, which have a lower risk of adverse events than the AAPs.

- The P&T Committee strongly recommends education of providers regarding the lack of evidence to support use of AAPs for primary insomnia and revision of current theater guidance (MOD-10).

7. With regards to safety, a black box warning applies to the entire class precluding use in elderly patients with behavioral and psychological symptoms of dementia due to increased mortality risk.
8. AAPs have different tolerability profiles as noted below:
   - Extrapyramidal symptoms are most likely to occur with risperidone (higher doses), paliperidone, and asenapine; and are least likely to occur with quetiapine, ziprasidone, aripiprazole, iloperidone and olanzapine.
   - Diabetes and weight gain are most commonly associated with clozapine and olanzapine. These effects are less common with aripiprazole, lurasidone, and ziprasidone.
   - Hyperprolactinemia has been most commonly associated with risperidone and paliperidone. Aripiprazole, iloperidone, and quetiapine have the lowest risk of this adverse event.
   - QTc interval prolongation is a concern with ziprasidone and iloperidone, but is least likely to occur with aripiprazole and lurasidone.
9. Adverse events are usually dose dependent and can be potentiated by patient characteristics such as age and comorbid conditions. AAP receptor binding affinities are associated with individual adverse events. Overall, the benefits conferred by AAPs are offset by limiting adverse effects.
10. For the pediatric population, the AAPs differ in their FDA-approved indications and ages. Aripiprazole, olanzapine, risperidone, paliperidone, and quetiapine are approved for use in pediatrics.
11. In a request for provider opinion, most respondents wanted 4 or more AAPs on their local formulary. In addition to risperidone, most respondents requested aripiprazole and quetiapine for inclusion on the BCF.
12. The clinician's choice for selecting an AAP should be influenced by the relationship between the efficacy and tolerability profile of the drug as well as individual patient characteristics.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the AAP Drug Class. Although there are differences within the drug class regarding safety and tolerability profiles, CMA and budget impact analyses (BIA) were conducted, since clinically relevant differences in efficacy for schizophrenia are not apparent Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA and BIA were used to assess the potential impact of cost scenarios where selected AAPs—aripiprazole (Abilify, Abilify Discmelt), asenapine (Saphris), clozapine (Clozaril, generics; Fazaclo), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine IR and ER (Seroquel IR, Seroquel XR), risperidone (Risperdal, Risperdal ODT), and ziprasidone (Geodon)—were designated with formulary or NF status on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.

Relative Cost Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) BIA results for the AAP agents showed that all investigated scenarios resulted in lower cost estimates compared to current MHS expenditures. Overall cost analyses indicated the most cost-effective scenario and operationally-appropriate choice placed clozapine (Clozaril, generics; Fazaclo), risperidone (Risperdal, Risperdal ODT, generics), aripiprazole (Abilify, Abilify Discmelt), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine (Seroquel; Seroquel XR), and ziprasidone (Geodon) on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (9 for, 6 against, 2 abstained, 0 absent) clozapine (Clozaril, generics; Fazlaco), risperidone (Risperdal, Risperdal ODT, generics), aripiprazole (Abilify, Abilify Discmelt), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine (Seroquel; Seroquel XR), and ziprasidone (Geodon) remain formulary on the UF. The P&T Committee recommended iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda) be designated NF on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 against, 1 abstained, 0 absent) to maintain risperidone (Risperdal, Risperdal ODT, generics), quetiapine IR (Seroquel), and quetiapine XR (Seroquel XR) on the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of iloperidone (Fanapt), asenapine (Saphris), lurasidone (Latuda), and the conditions for establishing MN for NF medications, the P&T Committee recommended (16 for, 0 against, 1 abstained, 0 absent) MN criteria for iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda). (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 against, 2 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is October 5, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Nasal Allergy Drugs (NADs)

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the NADs. The nasal corticosteroids were previously reviewed in November 2005, August 2007, and November 2008. The class is comprised of three subclasses as listed below.

- *Nasal Corticosteroids*: beclomethasone (Beconase AQ), budesonide (Rhinocort AQ), ciclesonide (Omnaris), flunisolide (generics), fluticasone furoate (Veramyst), fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and triamcinolone (Nasacort AQ)
- *Nasal Antihistamines*: azelastine 0.1% (Astelin, generic), azelastine 0.15% with sucralose and sorbitol (Astepro), and olopatadine (Patanase)
- *Nasal Anticholinergics*: ipratropium (Atrovent, generics)

Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

In terms of numbers of prescriptions dispensed, fluticasone propionate (Flonase, generics) is the highest utilized nasal allergy drug in the MTFs, followed by mometasone (Nasonex), and azelastine 0.1% (Astelin). This utilization pattern is also seen in the Retail Network. The current BCF drug for the NAD Drug Class is azelastine 0.1%; fluticasone propionate was removed from the BCF in May 2010 due to supply issues.

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

Nasal Corticosteroids:

With regards to efficacy/clinical effectiveness of the nasal corticosteroids, the following conclusions were made:

- FDA-approved indications—The P&T Committee recognized that there were minor differences among the drugs with regard to FDA-approved uses for seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), prophylaxis of allergic rhinitis (AR) symptoms, nonallergic rhinitis, and nasal polyps. Additionally, the pediatric FDA-approved age ranges differ between the products.
- Clinical Practice Guidelines—Evidence-based guidelines from the 2008 American Academy of Allergy, Asthma and Immunology (AAAAI) and 2010 Allergic Rhinitis and its Impact on Asthma (ARIA) consider the nasal corticosteroids as the most effective drug class at reducing allergic rhinitis symptoms of sneezing, rhinorrhea, nasal congestion, and itching.

- Pharmacodynamic/pharmacokinetic properties—The AAAAI guidelines concluded that despite differences in topical potency, lipid solubility, receptor binding affinity, and systemic bioavailability, the overall clinical response does not appear to vary significantly between drugs.
- Efficacy for SAR/PAR—There was no compelling new data to change the conclusion from the 2008 P&T Committee Meeting review, which established there is no evidence of clinically relevant differences between the agents at relieving nasal or ocular symptoms of AR. However, ciclesonide lacks published evidence for reducing ocular symptoms.
- Nasal polyps—Mometasone and beclomethasone are FDA-approved for nasal polyps.
- There was no compelling new evidence to change previous conclusions.

With regards to regards to safety and tolerability, the following conclusions were made:

- Local effects—Nasal irritation, epistaxis, and rhinorrhea are the most common local adverse effects and are equally likely to occur with any of the nasal corticosteroids.
- Systemic effects—For systemic effects of hypothalamic pituitary adrenal-axis suppression, growth suppression, and ocular adverse events (cataracts/glaucoma), there is insufficient evidence to determine whether one nasal corticosteroid is more likely to cause these effects than another. When given in recommended doses, the nasal corticosteroids are not generally associated with clinically significant systemic adverse effects.
- Tolerability and patient preferences—Patient preferences may play a role in differentiating between the nasal corticosteroids. However, the available clinical data is poor, and no nasal corticosteroid has proven superior to the others in patient preference trials. Nevertheless, flunisolide is poorly tolerated and must be dosed three or four times daily while the others are dosed once or twice daily. Budesonide (Rhinocort AQ) is the only nasal corticosteroid with a pregnancy category B rating by the FDA. All the nasal corticosteroids have a class labeling that these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nasal Antihistamines:

With regards to efficacy/clinical effectiveness of the nasal antihistamines, the following conclusions were made:

- FDA-approved indications—The P&T Committee recognized that there were minor differences between olopatadine (Patanase), azelastine 0.1% (Astelin, generic), and azelastine 0.15% (Astepro) with regard to FDA-approved uses for SAR and nonallergic rhinitis [e.g., vasomotor rhinitis (VMR)], and pediatric approval.
- Clinical Practice Guidelines—The 2010 ARIA guidelines suggest use of non-sedating oral antihistamines preferentially to nasal antihistamines. The 2008 AAAAI guidelines state that nasal antihistamines are generally less effective than nasal corticosteroids for treating AR, but may be considered for use as first-line treatment for AR and nonallergic rhinitis. Nasal antihistamines are associated with a clinically significant effect on reducing nasal congestion.
- Efficacy for SAR—Azelastine and olopatadine are superior to placebo in relieving symptoms of SAR. There is no new compelling clinical data to suggest one product is more efficacious than the others.
- Head-to-head study—One head-to-head trial comparing the use of olopatadine with azelastine found no difference in relief of nasal symptoms, but suggests that olopatadine may be better tolerated by patients, as shown by a lower incidence of bitter taste.

With regards to safety and tolerability of the nasal antihistamines, the following conclusions were made:

- Local adverse effects—Somnolence is considered a class effect (AAAAI guidelines). Bitter taste has a higher incidence with azelastine, while epistaxis occurred with roughly equal frequency between olopatadine and azelastine.
- Patient preferences and tolerability—The available clinical data is sparse and is limited to manufacturer-sponsored studies, but tends to favor olopatadine. However, there is insufficient evidence to definitively conclude that clinically relevant differences exist between the nasal antihistamines.

Nasal Anticholinergics:

With regards to efficacy/clinical effectiveness, safety, tolerability, and other factors, of the ipratropium nasal spray (Atrovent, generics), the following conclusions were made:

- FDA-approved indications—Ipratropium is solely indicated for the relief of SAR in adults and children 12 years of age and older.
- Clinical Practice Guidelines—2010 AAAAI guidelines state that nasal anticholinergics may effectively reduce rhinorrhea, but have no effect

on other nasal symptoms. Although adverse events are minimal, dryness of the nasal membranes may occur.

- Efficacy and Safety—No new efficacy or safety data have been published since the prior review. Ipratropium is rated Pregnancy Category B by the FDA.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the NADs. CMAs and BIAs were performed based on findings that there were no clinically relevant differences in efficacy, safety, tolerability, and other factors among the NADs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA and BIA were used to assess the potential impact of cost scenarios where selected nasal allergy agents were designated as formulary or nonformulary on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

BIA results for the NADs showed that six out of seven investigated scenarios resulted in lower cost estimates than current MHS expenditures. Scenarios where generic fluticasone propionate was selected as a BCF agent, with branded agents olopatadine (Patanase) and mometasone (Nasonex) on the UF were the most cost-effective scenarios overall. Sensitivity analysis results supported the above conclusion unless generic fluticasone propionate becomes unavailable for an extended period of time.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NADs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstained, and 0 absent) to recommend that:
    a) Fluticasone propionate (Flonase, generics), flunisolide (generics), mometasone (Nasonex), azelastine 0.1% (Astelin, generic), olopatadine (Patanase), and ipratropium (Atrovent, generics) be classified as formulary on the UF.
    b) Azelastine 0.15% (Astepro), beclomethasone (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), and triamcinolone (Nasacort AQ) remain designated as nonformulary under the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee considered the BCF status of the NADs. Based on the results of the clinical and cost evaluations presented, the P&T Committee voted (16 for, 0 opposed, 1 abstained, and 0 absent) to recommend that fluticasone propionate (Flonase, generics) be designated with BCF status. As a result of this action, azelastine 0.1% (Astelin, generics) is no longer designated with BCF status. Implementation would occur immediately on signing of the May 2011 P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. UTILIZATION MANAGEMENT

A. Sumatriptan (Alsuma)—QUANTITY LIMITS (QLs): A new sumatriptan autoinjection (Alsuma) is now marketed. Alsuma will be reviewed as a new FDA-approved drug in the triptan drug class at an upcoming P&T Committee meeting. QLs are currently in place for both oral and other injectable formulations of sumatriptan (Imitrex, generics; Sumavel) and the other oral triptans, which are consistent with their product labeling.

COMMITTEE ACTION: QL—The P&T Committee voted (16 for, 0 against, 1 abstain, 0 absent) to recommend QLs of 24 units/90 days in the mail order pharmacy and 8 units/30 days in the retail network, which is consistent with the recommended dosing from the product labeling and avoids breaking apart packages for dispensing.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Buprenorphine Transdermal System (Butrans)—QL: A transdermal formulation of buprenorphine is now available. Buprenorphine transdermal system (Butrans) is FDA-approved for management of moderate-to-severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. The manufacturer's dosing recommendation mandates one transdermal system for seven days. Butrans will be reviewed as a new FDA-approved drug in the narcotic analgesics drug class at an upcoming P&T Committee meeting.

1. ***COMMITTEE ACTION: QL***—The P&T Committee voted (16 for, 0 against, 1 abstain, 0 absent) to recommend QLs for transdermal buprenorphine of 12 patches/84 days in the mail order pharmacy and 4 patches/28 days in the retail network, which is consistent with the recommended dosing from the product labeling and will decrease the risk of inadvertent misuse of the product.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. ITEMS FOR INFORMATION

A. Dabigatran (Pradaxa)—Potential Prior Authorization: Dabigatran is the first oral anticoagulant to reach the market since warfarin (Coumadin). It is currently limited to use in patients with non-vavular atrial fibrillation to reduce the risk of stroke and systemic embolism. The P&T Committee reviewed the existing clinical data for dabigatran and its advantages and disadvantages versus warfarin. The P&T Committee also discussed whether prior authorization was required to ensure prescribing is consistent with the current FDA-approved indications. The P&T Committee agreed that Prior Authorization was not needed at this time. Dabigatran will be reviewed with the other anticoagulants at a future meeting.

B. PORT—The PORT updated the P&T Committee on their mission, and reviewed ongoing initiatives and studies.

C. Over-the-counter Fexofenadine (Allegra OTC)—Allegra is now available over-the-counter and does not require a prescription. Therefore, it is not covered under the TRICARE benefit. Fexofenadine (generic Allegra) is a covered benefit by prescription. However, raw material is not being supplied to the generic manufacturers. Therefore,

the supply of fexofenadine is diminishing. Once fexofenadine supplies are depleted, it is unlikely the medication will be available in the future.

VII. FUTURE CLASS OVERVIEWS

An overview of the antidepressants/pain drug class was presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important to use in completing the clinical effectiveness reviews and developing appropriate cost-effectiveness models. The clinical and economic analyses of this drug class will be presented at an upcoming meeting.

VIII. ADJOURNMENT

The meeting adjourned at 1615 hours on May 11, 2011, and at 1140 hours on May 12, 2011. The next meeting will be in August 2011.

Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix C—Table of Implementation Status of UF Recommendations/Decisions

Appendix D—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director

5 August 2011
(Date)

Appendix A—Attendance

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
LTC Travis Watson, MSC for COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
LCDR Tim Thompson	Navy, Pharmacy Officer (Pharmacy Consultant BUMED)
COL Ted Cieslak, MC	Army, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
LTC Amy Young, MC for LTC Bruce Lovins, MC	Army, Family Practice Physician
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Lt Col Sam Munro, MC	Air Force, Physician at Large
Mr. Joe Canzolino	Department of Veterans Affairs
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
CDR Michele Hupp, MSC	Defense Medical Standardization Board
Maj Achilles Hamilothoris	Defense Logistics Agency Troop Support

Appendix A—Attendance (continued)

Guests	
CAPT Nita Sood	Chief of Staff, TRICARE Management Activity/Pharmaceutical Operations Directorate
LCDR Jodi Sparkman	United States Public Health Service/Indian Health Service
Francine Goodman	VA PBM
MAJ Sandra Shelmerdine	Brooke Army Medical Center, Attending Psychiatrist
Capt Arnaldo Figueroa	Air Force Pharmacy Resident
Others Present	
COL Cynthia Clagett	DoD Pharmacoeconomic Center
CDR Joe Lawrence	DoD Pharmacoeconomic Center
Lt Col Rey Morales	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Asenapine (Saphris) Iloperidone (Fanapt) Lurasidone (Latuda) **Atypical Antipsychotics (AAPs)**	• The use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from the formulary alternatives • Formulary alternatives have resulted in therapeutic failure • Patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk
Beclomethasone (Beconase AQ) Budesonide (Rhinocort Aqua) Ciclesonide (Omnaris) Fluticasone furoate (Veramyst) Triamcinolone (Nasacort AQ) **Nasal Allergy Drugs (NADs)**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives.
Azelastine 0.15% with sorbitol and sucralose (Astepro) **Nasal Allergy Drugs (NADs)**	• Use of formulary alternatives is contraindicated

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary Table

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2011	**Atypical Antipsychotics**	UF Review	▪ Risperidone (Risperdal, Risperdal ODT, generics) ▪ Quetiapine (Seroquel, Seroquel XR)	▪ Aripiprazole (Abilify), Abilify discmelt ▪ Clozapine (Clozaril, Fazaclo, generics) ▪ Olanzapine (Zyprexa, Zydis) ▪ Paliperidone ER (Invega) ▪ Olanzapine/fluoxetine (Symbyax) ▪ Ziprasidone (Geodon)	▪ Asenapine (Saphris) ▪ Iloperidone (Fanapt) ▪ Lurasidone (Latuda)	Pending signing of minutes/ 60 days	None	Risperidone (all oral formulations including ODT) remains on the BCF along with quetiapine IR and ER
May 2011	**Nasal Allergy Drugs**	UF Review	▪ Fluticasone propionate (Flonase, generics)	*Nasal Corticosteroids* ▪ Flunisolide (generics) ▪ Mometasone (Nasonex) *Nasal Antihistamines* ▪ Azelastine 0.1% (Astelin, generic) ▪ Olopatadine (Patanase) *Anticholinergic* ▪ Ipratropium (Atrovent, generics)	*Nasal Corticosteroids* ▪ Beclomethasone dipropionate (Beconase AQ) ▪ Budesonide (Rhinocort Aqua), ▪ Ciclesonide (Omnaris) ▪ Fluticasone furoate (Veramyst) ▪ Triamcinolone acetonide (Nasacort AQ) *Anticholinergic* ▪ Azelastine 0.15% (Astepro)	Pending signing of minutes	No change to previous QLs	▪ Azelastine 0.1% (Astelin, generics) no longer BCF ▪ Olopatadine (Patanase) now UF
May 2011	**Benign Prostatic Hypertrophy (BPH) Alpha 1-Blockers (A1Bs)**	New Drug in Already Reviewed Class	*May 2010* ▪ Alfuzosin (Uroxatral) ▪ Tamsulosin (Flomax, generics) ▪ Terazosin (Hytrin; generics)	*May 2011* ▪ Tamsulosin/dutasteride (Jalyn) *May 2010* ▪ Doxazosin IR (Cardura; generics)	▪ Silodosin (Rapaflo) ▪ Doxazosin ER (Cardura XL)	Pending signing of minutes/ 60 days	See comments	Step Therapy (automated PA) with tamsulosin or alfuzosin as the preferred agents ▪ (Note: Step Therapy does not apply to terazosin, doxazosin, or doxazosin ER.)

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2011	**Ophthalmic-1 Agents**	New Drug in Already Reviewed Class	*August 2010* ▪ Olopatadine 0.1% (Patanol) ▪ Ketorolac 0.5% (Acular, generics)	***May 2011*** ▪ **Bromfenac QD (Bromday)** ***August 2010*** ▪ **Emedastine** (Emadine) ▪ Pemirolast (Alamast) ▪ Nedocromil (Alocril) ▪ Cromolyn (Crolom/Opticrom, generics) ▪ Lodoxamide (Alomide) ▪ Ketotifen (Zaditor, OTC) ▪ Bepotstine (Bepreve) ▪ Olopatadine 0.2% (Pataday) ▪ Azelastine (Optivar, generics) ▪ Epinastine (Elestat) ▪ Bromfenac BID (Xibrom) ▪ Ketorolac 0.4% (Acular LS, generics) ▪ Ketorolac 0.45% (Acuvail) ▪ Diclofenac (Voltaren, generics) ▪ Flurbiprofen (Ocufen, generics) ▪ Nepafenac (Nevanac)	▪ Not applicable (Bromday recommended for UF)	Pending signing of minutes	Not applicable	▪ Bromday QD formulation of bromefenac designated UF
Nov 2010	**Non-Insulin Diabetes Drugs** DPP-4 Inhibitors	New Drug in Already Reviewed Class	*Nov 2010* ▪ Sitagliptin (Januvia) ▪ Sitagliptin/Metformin IR (Janumet)	***May 2011*** ▪ **Saxagliptin/metformin ER (Kombiglyze XR)** *Nov 2010* ▪ Saxagliptin (Onglyza)	▪ Not applicable (Kombiglyze XR recommended for UF)	Pending signing of minutes/ 60 days	See comments	Step Therapy (automated PA) with metformin and sulfonylureas as step-preferred drugs

Appendix D—Table of Abbreviations

5-ARI	5-Alpha Reductase Inhibitor drug class
A1B	Alpha 1 Blocker drug class
AAAAI	American Academy of Allergy, Asthma, and Immunology
AAP	Atypical Antipsychotics drug class
AR	allergic rhinitis
ARIA	Allergic Rhinitis in Asthma
AUR	acute urinary retention
BCF	Basic Core Formulary
BPH	benign prostatic hypertrophy
BIA	budget impact analysis
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive behavioral therapy
CFR	Code of Federal Regulations
CMA	cost minimization analysis
CombAT	Combination of Avodart and Tamsulosin clinical trial
CPG	Clinical Practice Guidelines
DoD	Department of Defense
DHP	Dihydropyridine
DPP-4	dipeptidyl-peptidase-4
ECF	Extended Core Formulary
ER	extended release
FDA	U.S. Food and Drug Administration
FDC	fixed dose combination
HbA1C	Hemoglobin A1C
IR	immediate release
MDD	major depressive disorder
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NAD	Nasal Allergy Drug Class
NSAIDs	Non-steroidal Anti-inflammatory Drug Class
ODT	orally dissolving tablets
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	perennial allergic rhinitis
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
PTSD	post traumatic stress disorder
QL	quantity limit
Rxs	prescriptions
SAR	seasonal allergic rhinitis
SU	sulfonylurea
VA	Veterans Affairs
VMR	vasomotor rhinitis

ADDENDUM TO MAY 2011 MINUTES FOR DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

At the May 11–12, 2011, meeting, the Pharmacy and Therapeutics Committee, based on experience with the Uniform Formulary, changes in economic circumstances, and other appropriate factors, voted (14 for, 0 against, 3 abstain, 0 absent) to recommend an adjustment to the per prescription co-payments established in Title 32, Code of Federal Regulations, Section (Sec.) 199.21(i)(2). The proposed co-payment changes for tiers 1 (generic)/2 (formulary)/3 (non-formulary) are $5/$12/$25 for up to a 30-day supply at the Retail Network, and $0/$9/$25 for up to a 90-day supply at the Mail Order Pharmacy. These adjusted amounts maintain compliance with the requirements of Title 10, United States Code, Sec. 1074g(a)(6).

SUBMITTED BY:

John P. Kugler, M.D., MPH
Chair, Department of Defense Pharmacy
and Therapeutics Committee

DECISION ON RECOMMENDATIONS:

The recommended co-pay adjustment is approved effective October 1, 2011. For formulary and generic pharmaceutical agents obtained from a retail non-network pharmacy there is a 20 percent or $12.00 co-payment (whichever is greater) per prescription for up to a 30-day supply. For non-formulary pharmaceutical agents obtained at a retail non-network pharmacy there is a 20 percent or $25.00 co-payment (whichever is greater) per prescription for up to a 30-day supply.

Jonathan Woodson, M.D.
Assistant Secretary of Defense
(Health Affairs)

5 August 2011
(Date)

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
February 2011

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 16 and 17, 2011, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—Jonathon Woodson M.D. Director, approved the minutes for the November 2010 DoD P&T Committee meeting on February 4, 2011.

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Renin Angiotensin Antihypertensive Agents (RAAs)—Aliskiren/Amlodipine Tablets (Tekamlo)

Relative Clinical Effectiveness—Tekamlo is a fixed-dose combination product containing the direct renin inhibitor (DRI) aliskiren (Tekturna) and amlodipine (Norvasc, generics), a dihydropyridine (DHP) calcium channel blocker (CCB). Aliskiren is also available in a fixed-dose combination tablet containing the diuretic hydrochlorothiazide (HCTZ).

Aliskiren and aliskiren/HCTZ are currently designated with formulary status on the Uniform Formulary (UF), non-step-preferred, requiring prior authorization. Amlodipine is designated Basic Core Formulary (BCF). Tekamlo is included in the RAAs Drug Class, which is comprised of several subclasses: angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and direct renin inhibitors (DRIs) and their combinations with CCBs or diuretics. The RAAs Drug Class was reviewed at the August 2010 P&T Committee meeting. The clinical evaluation for Tekamlo included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Tekamlo is indicated for treating hypertension. No positive clinical outcomes have been reported for Tekamlo or any aliskiren-containing product, though outcomes trials

with aliskiren remain underway. Current national guidelines [Joint National Committee (JNC-7)] for treating hypertension have not yet addressed the place in therapy for DRIs, although updated guidelines (JNC-8) are anticipated later this year. The American Society of Hypertension does not list the Tekamlo (or any aliskiren-containing) combination as either preferred or acceptable in their recent position statement. Tekamlo does not contain a thiazide-type diuretic, which is considered first-line for most patients.

Treatment with Tekamlo was shown in one randomized trial to significantly reduce blood pressure (BP) compared to placebo. The adverse reaction profile for Tekamlo reflects that of the individual components.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) that although aliskiren/amlodipine (Tekamlo) has a unique mechanism of action due to the DRI component and offers the potential for increased medication persistence, it did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other RAAs included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of aliskiren/amlodipine (Tekamlo) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other RAAs, as well as the individual components, aliskiren and amlodipine. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost-minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of Tekamlo compared to other UF agents. Results from the CMA showed the projected weighted average cost per day for Tekamlo is higher than the other formulary RAAs, including the triple fixed-dose combination drug valsartan/amlodipine/HCTZ (Exforge HCT) and the individual components, Tekturna and amlodipine.

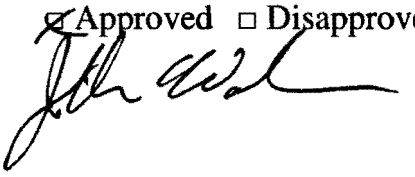
Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) aliskiren/amlodipine (Tekamlo) is not cost-effective relative to the other RAAs in this class

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) aliskiren/amlodipine (Tekamlo) be

designated with nonformulary (NF) status on the UF.

Director, TMA, Decision: ☑ Approved □ Disapproved

Approved, but modified as follows:



2. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—As a result of UF action, Tekamlo is designated as a non-preferred RAAs. Prior Authorization for the RAAs class requires a trial of one of the following step-preferred drugs for new patients: losartan (Cozaar, generics), losartan/HCTZ (Hyzaar, generics), telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT), telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), and valsartan/amlodipine/HCTZ (Exforge HCT). The other RAAs are non-preferred.

   The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria should apply to aliskiren/amlodipine (Tekamlo):

   a) Automated PA criteria:

      (1) The patient has received a prescription for losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT), telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any Military Health System (MHS) pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

      (2) The patient has tried one of the preferred RAAs and has had an inadequate response.

      (3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of aliskiren/amlodipine (Tekamlo) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Tekamlo. (See Appendix B for full MN criteria.)

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows

B. Renin Angiotensin Antihypertensive Agents (RAAs)—Olmesartan/ Amlodipine/HCTZ Tablets (Tribenzor)

Relative Clinical Effectiveness—Tribenzor is a fixed-dose combination product containing olmesartan (Benicar), amlodipine (Norvasc, generics), and HCTZ. It is the second three-drug combination product containing an ARB (olmesartan; Benicar), a DHP CCB (amlodipine), and thiazide-type diuretic (HCTZ) to reach the market. Exforge HCT [valsartan (Diovan)/amlodipine/HCTZ] was the first three-drug entrant on the market.

Olmesartan is currently designated with formulary status on the UF, non-step-preferred, requiring prior authorization; amlodipine and HCTZ are designated as BCF. Tribenzor is included in the RAAs Drug Class, which was reviewed at the August 2010 P&T Committee meeting. The clinical evaluation for Tribenzor included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Tribenzor is solely indicated for treating hypertension; it can be substituted for the individual titrated components or used as add-on therapy in patients not adequately controlled on two of the component drugs. It is not approved for initial therapy to control BP. Each of the component drugs is consistent with first-line therapy choices per current national guidelines (JNC-7).

Treatment with Tribenzor was shown in one randomized trial to significantly reduce BP when compared to baseline and to each two-drug combination of the component drugs. There are no trials evaluating clinical outcomes of mortality or morbidity with Tribenzor, although outcomes trials are available with the individual components.

The adverse reaction profile for Tribenzor reflects that of the individual components. Although no studies are available specifically addressing the potential for increased compliance with Tribenzor over the individual components administered together, other studies have shown an increase in persistence with fixed-dose antihypertensive combination products.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that although olmesartan/amlodipine/HCTZ (Tribenzor) offers the potential for increased medication persistence, it did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other RAAs included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of olmesartan/ amlodipine/HCTZ (Tribenzor) in relation to the efficacy, safety, tolerability, and clinical outcomes of the RAAs as well as the individual components, olmesartan, amlodipine, and HCTZ. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Tribenzor relative to other UF agents in this class. Results from the CMA showed the projected weighted average cost per day for Tribenzor is higher than the other formulary fixed-dose combination RAAs, including the triple-therapy drug amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) and the individual components olmesartan (Benicar), amlodipine, and HCTZ.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) olmesartan/amlodipine/HCTZ (Tribenzor) is not cost-effective relative to the other RAAs in this class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 2 absent) olmesartan/amlodipine/HCTZ (Tribenzor) be designated NF on the UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: PA CRITERIA***—As a result of the UF action, Tribenzor is designated as a non-preferred RAAs. The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) the same automated and manual PA criteria as outlined above for aliskiren/amlodipine (Tekamlo) should apply to olmesartan/amlodipine/HCTZ (Tribenzor). (See III, A, 2 for full PA criteria.)

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of olmesartan/amlodipine/HCTZ (Tribenzor) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Tribenzor. (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

C. Alzheimer's Drugs—Donepezil 23 mg Tablets (Aricept 23 mg)

Relative Clinical Effectiveness—Donepezil 23 mg (Aricept 23 mg) is a formulation of donepezil (Aricept) in a higher dosage than previously available (5, 10 mg). The Alzheimer's Drug Class was previously reviewed in November 2005; donepezil 5 and 10 mg tablets are the current Extended Core Formulary (ECF) drugs. Generic formulations of donepezil 5 and 10 mg tablets and orally disintegrating tablets (ODTs) entered the market in November 2010.

The pharmacokinetic profile of one donepezil 23 mg tablet shows a delayed and lower peak concentration compared to giving two of the 10 mg tablets. The 23 mg formulation is not an extended-release preparation; the 5 mg, 10 mg, and 23 mg tablets are administered once daily.

The one clinical trial used to gain FDA approval, which compared donepezil 23 mg with 10 mg, showed statistically significant improvement in measures of cognition, but no benefit in improving global functioning. An indirect comparison suggests efficacy of 23 mg donepezil appears similar to giving 10 mg donepezil with memantine (Namenda).

Tolerability of the donepezil 23 mg formulation will be limited by the increased incidence of adverse events, particularly gastrointestinal (GI) effects, compared with donepezil 10 mg.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) donepezil 23 mg (Aricept 23 mg) did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over donepezil 10 mg.

Relative Cost-Effectiveness—CMA was performed that evaluated the cost of donepezil 23 mg (Aricept 23 mg) in relation to other currently available agents in the Alzheimer's Drug Class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) donepezil 23 mg (Aricept 23 mg) tablets are currently cost competitive with all other comparators in the Alzheimer's Drug Class. However, the current generic manufacturer enjoys exclusive marketing rights until spring 2011. Once other generic manufacturers enter the market, donepezil 23 mg (Aricept 23 mg) tablets will be more costly than all other drugs in the Alzheimer's Drug Class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 4 opposed, 1 abstained, 0 absent) donepezil 23 mg tablets (Aricept 23 mg) be designated NF on UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of donepezil 23 mg tablets and the conditions for establishing MN for a NF medication, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Aricept 23 mg . (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3 ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Antiemetics—Ondansetron Soluble Film (Zuplenz)

Relative Clinical Effectiveness—Ondansetron oral soluble film (Zuplenz) is a serotonin subtype 3 (5-HT3) receptor antagonist. It is the only newer antiemetic available in an oral soluble film dosage form. Ondansetron (Zofran, generics) is also available in tablets, ODT, and an oral solution; these formulations are included on the UF. The Newer Antiemetics Drug Class was reviewed at the May 2006 P&T Committee meeting. There are no newer antiemetics designated as BCF; the older antiemetic promethazine is the only BCF antiemetic. The clinical evaluation included, but was not limited to, the requirements sated in 32 CFR 199.21(e)(1).

Ondansetron oral soluble film (Zuplenz) obtained FDA approval via section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using efficacy and safety data submitted from the ondansetron ODT (Zofran) submission. Bioequivalence studies demonstrated that a single dose of ondansetron oral soluble film 8 mg, taken with or without water and in underfed and fasting conditions, was comparable to ondansetron ODT 8 mg. There are no head-to-head clinical trials comparing ondansetron oral soluble film to the other newer antiemetics. Zuplenz's safety profile reflects that of the other ondansetron products.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) there is no evidence to suggest ondansetron oral soluble film (Zuplenz) has a compelling clinical advantage over ondansetron products currently included on the UF.

Relative Cost-Effectiveness—CMA was performed that evaluated the cost of ondansetron oral soluble film (Zuplenz) in relation to other currently available newer antiemetics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) ondansetron oral soluble film (Zuplenz) was more costly than all other oral comparators in the newer antiemetic class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) ondansetron oral soluble film (Zuplenz) be designated NF on the UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of ondansetron oral soluble film (Zuplenz) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Zuplenz. (See Appendix B for full MN criteria.)

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Approved

E. Self-Monitoring Blood Glucose System Test Strips—Glucocard 01, Glucocard Vital, Embrace, and NovaMax Test Strips

Relative Clinical Effectiveness—The self-monitoring blood glucose system (SMBGS) test strips were reviewed at the August 2008 P&T Committee meeting. SMBGS test strips designated with formulary status on the UF include Accu-Chek Aviva, Precision Xtra (the BCF SMBGS test strip), Freestyle Lite, Contour and TRUEtest. The clinical evaluation for Glucocard 01, Glucocard Vital, Embrace, and Nova Max test strips included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Glucocard 01, Glucocard Vital, Embrace, and Nova Max SMBGS test strips met the previously determined minimum technical requirements, which were approved at the May 2007 P&T Committee meeting. These 4 test strips also met the operational limitations of the existing Mail Order and Retail contracts, and Federal Government contracting regulations.

With regard to efficacy, the Glucocard 01, Glucocard Vital, Embrace, and Nova Max SMBGS test strips are accurate according to the requirements of the FDA and the International Standard for Organization, do not require manual coding, require only a 0.3–0.6 microliter blood sample size, are approved for at least one alternate testing site, and provide results in 5 to 7 seconds. The Glucocard 01, Glucocard Vital, Embrace, and Nova Max test strips utilize glucose oxidase instead of glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) as the reagent. Test strips with GDH-PQQ have rarely been associated with falsely high blood glucose readings and potential patient harm when used concurrently with products containing maltose (e.g., dialysis patients receiving icodextrin dialysate solutions).

The following did not meet the minimum technical requirements: Advocate Redi-code, EasyMax, EZ Smart Plus, Fifty50, Microdot, Rightest GS100, Rightest GS300, Ultratrak Ultimate. The following were not in compliance with the Buy American/Trade Agreement Acts: Blood Sugar Diagnostic, Liberty, Wavesense Jazz, Wavesense Presto.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent): 1) Glucocard 01, Glucocard Vital, Embrace, and Nova Max test strips are similar to the other test strips included on the UF, in terms of meeting the minimum technical requirements; 2) Nova Max test strips offer ketone testing on the Nova Max Plus meter (ketone testing is also available with the Precision Xtra meter); 3) Nova Max test strips offer wireless communication with insulin pumps on the Nova Max Link meter; and 4) Embrace test strips used in the Embrace meters offers a talking feature that speaks blood glucose results and instructions for testing.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of Glucocard 01, Glucocard Vital, Embrace, and Nova Max test strips in relation to efficacy, safety, tolerability, and clinical outcomes of the other test strips in the SMBGS test strip class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was performed to evaluate the cost-effectiveness of the Glucocard 01, Glucocard Vital, Embrace, and Nova Max SMBGS test strips. The cost-effectiveness of each new test strip was evaluated relative to the following agents: Accu-chek Aviva, Contour, OneTouch Ultra, Precision Xtra, and TRUEtest. CMA results showed the following, in order from most to least cost-effective: Glucocard Vital > Glucocard 01 > TRUEtest > Contour > Embrace > Precision Xtra > Accu-Chek Aviva > One Touch Ultra > Nova Max.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) 1) Glucocard Vital is the most cost-effective strip in all points of service, 2) Glucocard 01 is the second most cost-effective strip, 3) Embrace test strips fall in the middle of the price range for UF products and 4) Nova Max is the least cost-effective SMBGS test strip.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 2 absent):
    a) Glucocard 01, Glucocard Vital, and Embrace test strips be designated with formulary status on the UF;

    b) Nova Max be designated with NF status on the UF; and

c) Advocate Redi-code, Blood Sugar Diagnostic, EasyMax, EZ Smart Plus, Fifty50, Liberty, Microdot, Rightest GS100, Rightest GS300, Ultratrak Ultimate, Wavesense Jazz, and Wavesense Presto be designated with NF status on the UF because they do not meet the minimum technical standards required for inclusion on the UF or Federal Government contracting regulations.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: BCF RECOMMENDATION—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 2 absent) Glucocard 01, Glucocard Vital, and Embrace SMBGS test strips not be included in the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of the SMBGS and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Nova Max SMBGS test strips. (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60 days implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: QUANTITY LIMITS (QLs)***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the following QLs: 600 strips/90 days in the mail order pharmacy and 200 strips/30days in the retail network. These QLs are consistent with the other SMBGS test strips.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UF DRUG CLASS REVIEWS

A. Gastrointestinal-1 (GI-1) Drugs

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the GI-1 Drug Class. The class is comprised of three subclasses: aminosalicylates, GI steroids, and miscellaneous agents for irritable bowel syndrome (IBS). The aminosalicylates are comprised of sulfasalazine and the 5-aminosalicylate products (balsalazide, olsalazine, and mesalamine). The GI-1s have not been previously reviewed. There are no agents currently on the BCF; all drugs in the class are classified as UF drugs. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The individual GI-1s are listed below:

- **Aminosalicylates:** sulfasalazine (Azulfidine, generic), sulfasalazine enteric coated (EC) (Azulfidine EN, generic), balsalazide (Colazal,

generic), olsalazine (Dipentum), oral mesalamine (Asacol; Asacol HD; Pentasa; Lialda; Apriso), rectal mesalamine (Rowasa, generic enema; sulfite-free Rowasa enema; Canasa suppositories)

- **GI steroids:** budesonide (Entocort EC), rectal hydrocortisone (Colocort, Cortenema; Cortifoam)
- **Miscellaneous IBS agents:** alosetron (Lotronex), tegaserod (Zelnorm)

The GI-1 Drug Class expenditures exceed $60 million annually. In terms of overall utilization at all points of service, Asacol is the most utilized aminosalicylate and Entocort is the most utilized GI steroid. The miscellaneous agents for IBS have restrictive distribution and limited utilization within the MHS.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for the GI-1Drug Class:

- **Aminosalicylates:**
  1. Sulfasalazine, which is comprised of two molecules, sulfapyridine and 5-aminosalicylic acid (5-ASA), remains the first-line oral aminosalicylate recommended by the American College of Gastroenterology for extensive active ulcerative colitis. For the induction of remission in active ulcerative colitis, evidence from a systematic review by the Cochrane group found no clinically relevant differences in efficacy between sulfasalazine and the newer 5-ASA formulations.
  2. For maintenance of remission in ulcerative colitis, another systematic review showed a therapeutic advantage of sulfasalazine over the 5-ASA formulations. This advantage was offset by an increase in adverse events observed with sulfasalazine, due to the sulfapyridine moiety. The 5-ASAs are better tolerated than sulfasalazine since they lack the sulfa moiety.
  3. The newer 5-ASA formulations employ different release mechanisms to deliver drug at various sites in the GI tract. These differences in drug release and site of release do not confer additional benefits in terms of clinical response. All available 5-ASA formulations have shown superiority over placebo in treating ulcerative colitis. The lack of consensus in terms of efficacy measures for clinical trials makes it difficult to evaluate the comparative efficacy of the 5-ASAs.
  4. The efficacy of aminosalicylates in treating Crohn's disease is questionable. Though the aminosalicylates are often used in clinical practice for induction of mild to moderate Crohn's disease, a Cochrane

review showed minimal benefit over placebo and less effect compared to budesonide and conventional steroids.

5. In terms of safety, 5-ASAs, though not devoid of adverse reactions, are generally well tolerated. Olsalazine induces a secretory-type diarrhea, which largely limits its use. Otherwise, the safety profile is similar for the 5-ASA products. Concerns regarding renal toxicity, hepatotoxicity, and pancreatitis are idiosyncratic and equally projected across the 5-ASAs.
6. The choice of 5-ASA for treatment of ulcerative colitis will depend on other factors, such as location and extent of disease, as well as patient preference in terms of ease of administration, pill burden, and frequency of dosing.
7. Rectal 5-ASAs are useful in distal colitis. The choice between the liquid enema and suppositories is based on the extent of diseased colon. Current guidelines recommend combination of oral and rectal therapy for treating mild to moderate distal ulcerative colitis since combination therapy is more effective than either therapy alone.

- **GI steroids:**

1. Budesonide delayed-release capsules (Entocort EC) are the only oral steroid preparation available in the GI-1 Drug Class. Budesonide has fewer systemic effects than the other oral corticosteroids (e.g., prednisone) and is delivered directly to the colon. For induction of remission in Crohn's disease, a systematic review found oral budesonide was more effective than placebo and mesalamine, but corticosteroids were more effective than budesonide.
2. For the maintenance of remission in Crohn's disease, another systematic review found budesonide was no more effective than placebo after 6-12 months, and budesonide was no more effective than glucorticoids (which are not effective for maintaining remission). Budesonide was more effective at maintaining remission in Crohn's disease compared to mesalamine. The package labeling for Entocort EC limits treatment to 3 months.
3. Budesonide is not effective for maintenance of remission in ulcerative colitis, based on a systematic review comparing budesonide with placebo, oral mesalamine, and corticosteroids.
4. The rectally-administered topical steroids include the hydrocortisone enema (Colocort, Cortenema) and foam (Cortifoam) preparations,

which are effective and safe for the treatment of distal ulcerative colitis.

5. Treatment choice depends on the location of disease and tolerability of the preparation.

- **Miscellaneous IBS agents:**
  1. Due to severe adverse effects, including death due to bowel obstruction, alosetron (Lotronex) is restricted to women with severe refractory diarrhea-predominant IBS under an FDA-mandated risk evaluation and mitigation strategy program.
  2. Due to severe adverse cardiovascular effects, tegaserod (Zelnorm) is available only for emergency use in cases of severe constipation-predominant IBS after application to the FDA. Upon approval, the manufacturer sends the medication to the patient.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the GI-1 Drug Class. CMAs and budget impact analyses (BIAs) were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

- **Aminosalicylates:** CMA and BIA were used to assess the potential impact of cost scenarios where sulfasalazine (Azulfidine, generic), sulfasalazine EC (Azulfidine EN, generic), balsalazide (Colazal, generic), olsalazine (Dipentum), oral mesalamine (Asacol, Asacol HD, Apriso, Lialda, Pentasa), and rectal mesalamine (Canasa, Rowasa, sfRowasa) were designated with formulary or NF status on the UF. Cost scenarios evaluating the impact of designating selected agents with BCF status were also considered. BIA results showed that all investigated scenarios resulted in lower cost estimates compared to current MHS expenditures. Overall, cost analyses indicated that the placement of all agents on the UF was the most cost-effective scenario.

- **GI steroids and Miscellaneous IBS agents:** Cost analysis and budget estimates were used to assess the potential impact of designating budesonide (Entocort EC), and rectal hydrocortisone (Colocort, Cortenema, and Cortifoam) with formulary or NF status on the UF. Cost analysis results and budget estimates indicated that the placement of all agents on the UF was the most cost-effective scenario.

Relative Cost-Effectiveness Conclusions—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted to accept the relative cost-effectiveness of the aminosalicylates (17 for, 0 opposed, 0 abstained, 1 absent) and GI Steroids and Miscellaneous IBS agents (17 for, 0 opposed, 0 abstained, 1 absent) in the GI-1 Drug Class.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

   a) **Aminosalicylates:** sulfasalazine, balsalazide, olsalazine (Dipentum), mesalamine (Asacol, Asacol HD, Pentasa, Lialda, Apriso, Canasa, sulfite-free Rowasa, and mesalamine enema) remain classified with formulary status on the UF (15 for, 1 opposed, 1 abstained, 1 absent).

   b) **GI steroids and Miscellaneous IBS Agents:** budesonide (Entocort EC), hydrocortisone enema, hydrocortisone foam (Cortifoam) and alosetron (Lotronex) remain classified with formulary status on the UF (16 for, 0 opposed, 1 abstained, 1 absent). Tegaserod (Zelnorm) is only available from the FDA under a treatment investigational new drug application.

   c) As a result of the above recommendations, there are no GI-1 agents designated with NF status on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended:

   a) **Aminosaliclates:** Mesalamine (Asacol) be designated with BCF status upon signing of the minutes (15 for, 1 opposed, 1 abstained, 1 absent).

b) **GI steroids and Miscellaneous IBS agents:** None of the GI steroids or Miscellaneous IBS agents be added to the BCF (16 for, 0 opposed, 1 abstained, 1 absent).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Pancreatic Enzyme Products (PEPs)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the PEPs. There are three drugs in the class, which all contain the same active ingredient of lipase, protease, and amylase in different amounts. Creon and Zenpep were approved for marketing in 2009 and Pancreaze was approved in April 2010. There is one authorized generic PEP formulation, pancrelipase delayed-release capsules, which is equivalent to Zenpep 5,000. All previously marketed non-FDA approved PEPs have been discontinued.

The PEP Drug Class has not previously been reviewed; all the drugs are currently designated with formulary status on the UF. This class is designated as an ECF drug class. The clinical review focused on use of the PEPs for exocrine pancreatic insufficiency (EPI) and included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1). Creon has the highest utilization, with about 500,000 units dispensed monthly in the MHS, followed by Zenpep and Pancreaze at an estimated 100,000 units each dispensed monthly.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following clinical effectiveness conclusions for the PEPs:

1. There are no head-to-head trials comparing the PEPs. Based on indirect studies comparing each agent to placebo, Creon, Pancreaze, and Zenpep are superior to placebo for improving fat malabsorption associated with EPI due to cystic fibrosis (CF).
2. For patients with EPI due to CF, the endpoint of the average coefficient of fat absorption (CFA) for Creon, Pacnreaze, and Zenpep ranged between 83%–88% in the placebo-controlled trials used to obtain FDA approval. A

CFA > 80% is considered clinically relevant for improving fat malabsorption.

3. Creon was superior to placebo for improving fat malabsorption (measured by CFA) as compared to placebo in one study conducted in 44 patients with chronic pancreatitis or following pancreatectomy. Creon is the only PEP approved for use in patients with chronic pancreatitis. In contrast, Zenpep did not meet primary endpoint for improving fat malabsorption in 72 patients with chronic pancreatitis in one unpublished study.
4. With regards to safety, the available evidence suggests there are no clinically relevant differences between Creon, Pancreaze, and Zenpep.
5. With regards to other factors such as microsphere size and storage requirements/stability, there are no clinically relevant differences between the PEPs. Zenpep has unpublished information for enteral administration via G-tube administration, but this route of administration is currently under FDA review.
6. With regard to special populations, Pancreaze is the only PEP which has efficacy and safety data in children as young as 6 months. Pediatric dosing should follow Cystic Fibrosis Foundation Consensus Conferences guidelines.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the PEPs. Based on clinical findings that efficacy, safety, tolerability, and other factors found among the PEPs were similar at equipotent doses, CMA and BIA were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost-minimization analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) that Pancreaze was the most cost-effective PEP, followed by Zenpep. Creon was the least cost-effective agent based on weighted average cost per day of therapy. BIA results indicated the scenario that placed all PEPs on the UF was the most cost-effective formulary scenario.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) Creon, Pancreaze, and Zenpep be designated with formulary status on the UF. As a result of this action, no PEPs are designated NF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: ECF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 1 opposed, 1 abstained, 1 absent) Pancreaze be designated with ECF status upon signing of the minutes.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Antilipidemic-2s (LIP-2s)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the LIP-2 Drug Class, which was previously reviewed at the May 2007 P&T Committee meeting. The clinical review for the LIP-2s included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The LIP-2 Drug Class accounted for $111 million in MHS expenditures in FY 2010. This class is comprised of three subclasses: fibric acid derivatives, prescription omega-3 fatty acids, and bile acid sequestrants (BAS). For the omega-3 fatty acids (fish oil products), there are a number of nutritional supplement products available over-the-counter (OTC); they are not eligible for inclusion on the UF. The individual drugs are outlined, below.

- **Fibric acid derivatives:** gemfibrozil (Lopid, generics) and several formulations of fenofibrate (Tricor; Lofibra, generics; Antara, Lipofen and Triglide), fenofibrate acid (Fibricor), and choline fenofibrate acid (Trilipix)
- **Prescription Omega-3 fatty acids:** Lovaza (formerly known by the brand name Omacor)
- **BAS:** cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and colesevelam (Welchol).

Gemfibrozil is the current LIP-2 BCF drug. The prescription omega-3 fatty acid product Lovaza, the BAS colesevelam (Welchol), and several fenofibrate formulations (including Tricor and Trilipix) are nonformulary.

Fenofibrate meltdose (Fenoglide) was removed from the BCF in November 2010 due to manufacturing problems. Subsequently, it was not covered by TRICARE® based on the manufacturer's refusal to sign a Master Agreement with the Veterans Administration and participate in the drug discount program required by 38 United States Code 8126. Additionally, the manufacturer voluntarily removed Fenoglide from the TRICARE Pharmacy Benefits Program.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following clinical effectiveness conclusions for the LIP-2s:

- **Fibric acid derivatives:**
  1. Both gemfibrozil and fenofibrate reduce triglycerides (TG) 20%–50% and raise high density lipoprotein (HDL) 10%–20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.
  2. In terms of clinical outcomes, there are no head-to-head trials comparing gemfibrozil with fenofibrate. Gemfibrozil was shown in two trials (HHS and VA-HIT trials) to reduce nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death. Mixed results have been shown with fenofibrates. A reduction in nonfatal MI was seen with fenofibrates in the FIELD trial, but there was a nonsignificant increase in CHD death. In the ACCORD trial when fenofibrate was used in combination with a statin, there was a trend for a reduction in nonfatal MI, nonfatal stroke or death from cardiovascular (CV) causes in individuals with TG > 204 mg/dl and HDL < 34 mg/dl.
  3. The newer fenofibrate formulations [nanocrystallized (Tricor), micronized (Antara and Lofibra), insoluble drug-delivery particle (IDD-P) (Triglide), meltdose (Fenoglide), and lidose (Lipofen)] utilize distinct technologies to enhance absorption. The fenofibric acid products (Trilipix and Fibricor) are prodrugs which are water soluble. Despite differences in dosage strength, particle technology, or active ingredient, the fenofibrates are bioequivalent to the original Tricor 200 mg formulation approved in 1988. In terms of efficacy, these newer fenofibrate formulations do not offer a clinical advantage over the original Tricor fenofibrate formulation. The newer fenofibrate formulations do offer patient convenience of administration

without regard to meals and once daily dosing, which compares with gemfibrozil.

4. Fenofibrate acid (Trilipix) is the only fenofibrate indicated for combination use with a statin, but other fenofibrate formulations are frequently given concurrently with a statin.
5. Gemfibrozil and the fenofibrates have similar drug-drug interaction profiles and contraindications. Tolerability issues that may affect patient compliance include GI distress (abdominal pain, constipation, nausea, etc.). Gemfibrozil must be taken twice daily prior to meals.
6. The ACCORD trial demonstrated the combination of a fenofibrate with a statin was well tolerated. Although pharmacokinetic and FDA spontaneous adverse event reporting data suggest that gemfibrozil is more likely to interact with statins than fenofibrates, there is a lack of clinical evidence to support that the incidence of myopathy/rhabdomyolysis is lower with fenofibrates. Current guidelines from the American Heart Association and the American College of Cardiology conclude there is a risk with all fibric acid and statin combinations that is not limited to just gemfibrozil.
7. For MHS patients requiring a fibric acid derivative, gemofibrozil and at least one fenofibrate formulation would be expected to meet the needs of the majority of the patient population.

- **Omega-3 fatty acids:**

1. Lovaza is the only prescription omega-3 fatty acid product approved by the FDA. It is indicated for use as an adjunct to diet in patients with very high TG levels (>500 mg/dL).
2. FDA oversight of the manufacturing process for Lovaza offers increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.
3. Overall, Lovaza decreases TG 20%–45%. However, Lovaza has also been associated with increases in low density lipoprotein (LDL), which may offset the beneficial reductions in TG.
4. Lovaza's TG-lowering effects are slightly lower than those achieved with fibric acid derivatives or niacin. Lovaza is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

5. There are no head-to-head trials comparing Lovaza with fish oil supplements to evaluate lipid profile changes. Trials with fish oil supplements show they are effective at reducing TG levels at doses ranging between 2–4 grams/day.
6. The Lovaza product marketed in the United States does not have outcomes studies showing beneficial effects of reducing death, MI, or stroke, and is not indicated to prevent CHD. The evidence of fish oil supplements or dietary fish consumption for reducing CHD risk is supportive but not conclusive.
7. There is insufficient evidence to support the use of Lovaza for non-CV conditions, including behavioral health/psychiatric conditions. The results of small clinical trials have been conflicting, and used formulations of fish oil different than that found in the Lovaza product.
8. GI disturbances and taste perversions are the most commonly reported adverse effects of Lovaza.
9. There are a few OTC fish oil supplements available from reputable manufacturers that contain the equivalent ingredients per capsule as Lovaza, which should yield similar clinical results. But concerns remain regarding issues such as potency, capsule counts, batch-to-batch consistency, and purity/ truth in labeling with the fish oil supplements.
10. Lovaza provides an alternative therapy in patients with elevated TGs who are not candidates for niacin or fibrates due to a history of adverse effects.

- **BAS:**

1. The BAS reduce LDL 15%–30%. This subclass has largely been replaced by the statins, which reduce LDL 18%–55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL. Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.
2. In terms of lipoprotein effects, colesevelam (Welchol) has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B versus C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.
3. Colesevelam (Welchol) is now FDA-approved for glycemic control in patients with Type 2 diabetes mellitus, when used as adjunctive therapy with other glucose-lowering drugs. Colesevelam only provides a modest HbA1c reduction and other noninsulin diabetes drugs reduce HbA1c more than 0.5%.

4. Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of LIP-2 Drug Class. CMAs and BIAs were performed based on findings that there were no clinically relevant differences in efficacy, safety, tolerability, and other factors among the LIP-2 subclasses. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

- **Fibric acid derivatives:** BIA was used to assess the potential impact of cost scenarios where selected fibric acid derivatives were designated with formulary or NF status on the UF. Cost scenarios evaluating the impact of designating selected agents with BCF and step-preferred statuses were also considered. BIA results for the fibric acid derivatives subclass showed that all investigated scenarios resulted in lower cost estimates than current MHS expenditures. Overall, scenarios where fenofibrate nanocrystallized (Tricor), generic gemfibrozil, and generic fenofibrate micronized/non-micronized were selected as step-preferred agents, while designating all other fibric acids as UF, were the most cost-effective scenarios. A sensitivity analysis was performed regarding the date of generic competition for fenofibrate nanocrystallized (Tricor) and fenofibric acid choline (Trilipix). Sensitivity analysis results supported the above conclusion.
- **Omega-3 fatty acids:** BIA was used to assess the potential impact of cost scenarios where Lovaza was designated with formulary or NF status on the UF. Cost scenarios evaluating the impact of implementing prior authorization were also considered. Overall, scenarios where Lovaza was subject to a prior authorization, which would apply to all current and new users, were the most cost-effective. Results from a sensitivity analysis performed supported the above conclusion.
- **BAS:** Results from CMAs performed showed colesevelam (Welchol) was less cost effective than generic BAS currently available on the UF.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted to accept the relative cost-effectiveness of the fibric acid derivatives (17 for, 0 opposed, 0 abstained, 1 absent), prescription omega-3 fatty acids (Lovaza) (16 for, 0 opposed, 0 abstained, 2 absent), and BAS (17 for, 0 opposed, 0 abstained, 1 absent) in the LIP-2 Drug Class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

   a) **Fibric Acid Derivatives:**

      (1) Gemfibrozil (Lopid, generics), fenofibrate IDD-P (Triglide), fenofibrate micronized/nonmicronized (Lofibra, generics), and fenofibrate lidose (Lipofen) remain designated with formulary status on the UF; and that fenofibrate micronized (Antara) fenofibrate nanocrystallized (Tricor), fenofibric acid (Fibricor), and choline fenofibric acid (Trilipix) be designated with formulary status on the UF (16 for, 0 opposed, 0 abstained, 2 absent).

      (2) Prior authorization for the fenofibrate acid derivatives would require a trial of gemfibrozil, generic fenofibrate micronized/nonmicronized formulations (including Lofibra), or fenofibrate nanocrystallized (Tricor) (step-preferred drugs) for new patients (16 for, 0 opposed, 0 abstained, 2 absent).

   b) **Omega-3 fatty acids**: Lovaza be designated with formulary status on the UF (12 for, 4 opposed, 1 abstained, 1 absent) and subject to PA criteria that allows use in all current and new users, only for FDA-approved indications.

   c) **Bile Acid Sequestrants:** Cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), and colestipol (Colestid, generics) remain formulary on the UF; and, colesevelam (Welchol) remain designated with NF status on the UF (14 for, 2 opposed, 1 abstained, 1 absent).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T

Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 0 abstained, 2 absent) gemfibrozil and fenofibrate nanocrystallized (Tricor) be designated with BCF status.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: FIBIC ACID DERIVATIVES PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) the following PA criteria should apply to the nonpreferred fibric acid derivatives, fenofibrate micronized (Antara), fenofibrate IDD-P (Triglide), fenofibrate micronized (Lipofen), fenofibric acid (Fibricor), and fenofibric acid choline (Trilipix). Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for gemfibrozil, generic fenofibrate micronized/nonmicronized formulations (including Lofibra) or fenofibrate nanocrystallized (Tricor) (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has a contraindication to the preferred fibric acid derivatives that is not expected to occur with the nonpreferred fibric acid derivatives.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: FIBRIC ACID DERIVATIVES PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter

to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5. ***COMMITTEE ACTION: LOVAZA PA CRITERIA***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to the prescription omega-3 fatty acid product, Lovaza. Lovaza would be approved only for the FDA-approved indications. All current and new users of Lovaza must meet one of the following criteria to pass through the PA process.

   a) Patients with TG > 500 mg/mL who are receiving statins AND have had an inadequate TG-lowering response to a therapeutic trial of niacin (1-2 g/day) or fibrates, are unable to tolerate niacin or fibrates, or are not candidates for niacin or fibrate therapy.

   b) Patients with TG > 500 mg/mL who are not receiving statins AND who have had an inadequateTG-lowering response to a therapeutic trial of monotherapy with both a fibrate and niacin, are unable to tolerate niacin and fibrates, or are not candidates for niacin and fibrate therapy.

   c) Coverage is not approved for Lovaza for use in non-FDA approved conditions, including the following: Attention Deficit Hyperactivity Disorder, Alzheimer's disease, bipolar disease, Crohn's disease, cystic fibrosis, dementia, depression, inflammatory bowel disease, intermittent claudication, metabolic syndrome, osteoporosis, post-traumatic stress disorder, renal disease (immunoglobulin A nephropathy), rheumatoid arthritis, schizophrenia, Type 2 diabetes mellitus, and ulcerative colitis.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

6. ***COMMITTEE ACTION: LOVAZA PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 3 opposed, 1 abstained, 1 absent) 1) an

effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the Committee's recommendation the effective date is July 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

7. ***COMMITTEE ACTION: WELCHOL MN CRITERIA***—Based on the clinical evaluation of the BAS and the conditions for establishing MN for a NF medication, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) maintaining the current MN criteria for colesevelam (Welchol). (See Appendix B for full MN criteria.)
   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

V. BASIC CORE FORMULARY ISSUES—TRIPTAN BCF CLARIFICATION

The Triptan Drug Class was reviewed in June 2008. At that time, rizatriptan (Maxalt) was designated with BCF status upon signing of the minutes, and sumatriptan oral tablets and one injectable formulation would be added to the BCF when cost-effective multisource generic formulations became available. The cost of generic formulations of sumatriptan tablets has decreased. The cost of generic formulations of sumatriptan injection is lower than the branded products, but is still more expensive than the tablet formulations.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) upon signing of the minutes, to:
   a) maintain rizatriptan tablets on the BCF; and
   b) add sumatriptan tablets to the BCF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT—QUININE SULFATE (QUALAQUIN) QLs

Quinine sulfate, under the trade name Qualaquin, is FDA-approved only for the treatment of malaria. Qualaquin's product labeling states it is not approved for malaria prophylaxis or for persistent malaria. Recommended dosing for treatment of malaria is 2 capsules, 3 times daily, for 7 days. Center for Disease Control recommendations for quinine use include co-administration with tetracycline, doxycycline, or clindamycin, dependent on the type of plasmodium species and the resistance patterns in each malaria-endemic country. In May 2010, the P&T Committee recommended a prior authorization requirement for Qualaquin, limited to treatment of malaria, due to severe adverse events, including death. The PA took effect on October 6, 2010.

1. ***COMMITTEE ACTION: QUANTITY LIMIT***—To ensure the appropriate use of Qualaquin, consistent with the product labeling, the P&T Committee recommended (16 for, 2 opposed, 0 abstained, 0 absent) implementing a quantity limit of 42 capsules per fill, one fill per prescription, with no refills, which will allow quinine (Qualaquin) use in patients who meet the following criteria:

   a) a documented diagnosis of malaria.

   The quantity limits for Qualaquin become effective the first Wednesday after a 60-day implementation period in all points of service. Based on the Committee's recommendation the effective date is July 13, 2011.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

VII. ITEMS FOR INFORMATION

A. Use of Non-Insulin Diabetes Drugs in the MHS—DoD Pharmacy Outcomes Research Team (PORT)

As a follow-up to the November 2010 review of non-insulin diabetes drugs, the PORT presented analysis of HbA1c levels among 6,947 MTF patients who were new users of specific subclasses of oral non-insulin diabetetes drugs [metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl-peptidase 4 (DPP-4s), or glucagon-like peptide-1 receptor agonists (GLP1RAs)] from July 2008 to December 2008. Findings suggested appropriate use of the newer agents, with DPP-4s and GLP1RAs being used generally as third- or fourth-line therapy. Additionally, the percentage of new DPP-4 or GLP1RA users with HbA1c > 10 (who will probably require insulin therapy rather than an additional oral non-insulin diabetes drug to reach HbA1c goal) was similar to that found among new users of metformin, sulfonylureas, or TZDs. The P&T Committee agreed that the analysis provides a baseline for future drug utilization review, following addition of sitagliptin (Januvia) and sitagliptin/ metformin (Janumet) to the BCF.

B. Propoxyphene Withdrawal from the Market—Propoxyphene has been available since the late 1950s, but concerns regarding adverse events, including prolongation of the QT interval have persisted. All propoxyphene products (Darvon, Darvocet, generics) were voluntarily withdrawn from the market in November 2010.

VIII. FUTURE CLASS OVERVIEWS

Overviews for four drug classes were presented to the P&T Committee. Multiple sclerosis-disease modifying drugs were reviewed in May 2005, the contraceptives drug class was reviewed in May 2006, and the short-acting beta agonists were reviewed in November 2008. Information regarding the non-steroidal anti-inflammatory drugs (NSAIDs) drug class was also presented; this class includes the cyclooxygenase-2 selective NSAIDs. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing appropriate cost-effectiveness models. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

IX. ADJOURNMENT

The meeting adjourned at 1620 hours on February 16, 2011, and at 1200 hours on February 17, 2011. The next meeting will be in May 2011.

Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix C—Table of Implementation Status of UF Recommendations/Decisions

Appendix D—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Jonathan Woodson, M.D.
Director MAY 9 2011

(Date)

Appendix A—Attendance

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Dennis Alder for CAPT Vernon Lew	Coast Guard, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
LTC Daniel Hsu, MC for COL Ted Cieslak, MC	Army, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
CAPT David Tanen, MC	Navy, Physician at Large
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LTC Amy Young, MC for LTC Bruce Lovins, MC	Army, Family Practice Physician
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Mr. Joe Canzolino	Department of Veterans Affairs
Dr. Miguel Montalvo	TRICARE Regional Office-South Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present	
Mr. David Hurt	Associate General Counsel, TMA
CDR Jay Peloquin	Defense Logistics Agency Troop Support
Guests	
Dr. Mark Geraci	Department of Veterans Affairs
LCDR Jodi Sparkman	United States Public Health Service/Indian Health Service

Appendix A—Attendance (continued)

Guests	
Lt Col Larry Gudgel	Wilford Hall Medical Center
LCDR Heather Hellwig	Navy Pharmacy Resident
Others Present	
COL Cynthia Clagett	DoD Pharmacoeconomic Center
Lt Col Rey Morales	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Colesevelam (Welchol) **Antilipidemic-2s** (No change in MN criteria from May 2007)	• The use of BOTH of the following formulary alternatives is contraindicated: cholestyramine and colestipol • The patient has experienced or is likely to experience significant adverse effects from BOTH of the following formulary alternatives: cholestyramine and colestipol • BOTH of the following formulary alternatives have resulted in therapeutic failure: cholestyramine and colestipol • The patient has a history of GI obstruction and requires treatment with a BAS. • The patient is pregnant and requires treatment with a BAS.
Donepezil 23 mg (Aricept 23 mg) **Alzheimer's Drugs**	• Use of formulary agents has resulted in therapeutic failure.
Ondansetron oral film (Zuplenz) **Antiemetics**	• Use of formulary agents contraindicated • No alternative formulary agent available for pediatric patients who cannot take ondansetron ODT or patients with phenylketonuria (Zuplenz does not contain phenylalanine)
Aliskiren/amlodipine (Tekamlo) **Renin-Angiotensin Antihypertensives**	• Use of formulary agents contraindicated
Olmesartan/amlodipine/ hydrochlorothiazide (Tribenzor) **Renin-Angiotensin Antihypertensives**	• Use of formulary agents contraindicated • The patient previously responded to a nonformulary agent, and changing to a formulary agent would incur unacceptable risk
Novamax test strip **Self-monitoring Blood Glucose Test Strips**	• No alternative formulary agent available for patients using an insulin pump (for SMBGS that wirelessly communicate results to the pump only)

BAS: bile acid sequestrant; ODT: orally dissolving tablets; SMBGS: self-monitoring blood glucose test strips

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary Table

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2011	**Gastrointestinal-1s**	UF Review	**Aminosalicylates** ▪ Mesalamine (Asacol)	**Aminosalicylates** ▪ Sulfasalazine/EC (Azulfidine, Azulfidine EN generic) ▪ Balsalazide (Colazal, generic) ▪ Olsalazine (Dipentum) ▪ Mesalamine (Asacol, Asacol HD, Pentasa, Lialda, Apriso, Canasa, Rowasa, sfRowasa enema) **GI-Steroids** ▪ Budesonide (Entocort EC) ▪ Hydrocortisone enema and foam (Cortenema, generic; Cortifoam, generic) **Miscellaneous Agents** ▪ Alosetron (Lotronex)	▪ None	Pending signing of minutes	None	Asacol is the BCF agent for the class, all others remain formulary on the UF Note: Tegaserod (Zelnorm) is no longer commercially available; only available under treatment investigation new drug application to the FDA. If approved by FDA, sent directly to the patient by the manufacturer
Feb 2011	**Pancreatic Enzyme Products**	UF Review	▪ Pancreaze	▪ Creon ▪ Zenpep	▪ None	Pending signing of minutes	None	Pancreaze is the ECF selection for the class, all others remain formulary on the UF
Feb 2011	**Antilipidemic-2s** Previous UF review May 2006	UF Review	**Fibric Acid Derivatives** ▪ Gemfibrozil (Lopid, generics) ▪ Fenofibrate micronized/nonmicronized (Lofibra, generics) ▪ Fenofibrate nanocyrstallized (Tricor)	**Fibric Acid Derivatives** ▪ IDD-P (Triglide) ▪ micronized (Antara) ▪ lidose (Lipofen) ▪ Fenofibric acid (Fibricor) ▪ Choline fenofibric acid (Trilipix) **Prescription Omega-3 Fatty Acids** ▪ Lovaza **Bile Acid Sequestrants** ▪ Cholestyramine/ sucrose/aspartame (Questran, Questran Light, generics) ▪ Colestipol (Colestid, generics)	**Bile Acid Sequestrants** ▪ colesevelam (Welchol) remain NF (originally designated NF in May 2006)	Pending signing of minutes 60 days for PA	**Fibric Acids** Automated PA rec for Lovaza **Omega-3 Fatty Acids** PA rec for Lovaza	**Fibric Acids** Trial of generic fenofibrates, gemfibrozil, or Tricor mandated prior to use of a non step-preferred Triglide, Antara, Lipofen, Fibricor, and Trilipix **Omega-3 Fatty Acids** PA restricting Lovaza usage to the FDA-approved indication for all patients, new and existing users

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2011	**Renin-Angiotensin Antihypertensive Agents (RAAs)** (previously reviewed Aug 2010)	• New Drug **RAAs/CCB** Olmesartan/amlodipine/HCTZ (Tribenzor) **DRIs** Aliskiren/ amlodipine (Tekamlo)	From August 2010 meeting: **ACE Inhibitors** ▪ Lisinopril (Prinvil, Zestril, generic) ▪ lisinopril HCT (Prinzide, Zestoretic generic) ▪ Captopril (Capoten, generic) ▪ Ramipril (Altace, generic) **ACE Inhibitor/CCB** ▪ Benazepril/amlodipine (Lotrel, generic) **ARBs** ▪ Losartan (Cozaar, generic) ▪ Losartan/HCTZ (Hyzaar, generic) ▪ Telmisartan (Micardis) ▪ Telmisartan/ HCTZ (Micardis HCT) ▪ Valsartan (Diovan) ▪ Valsartan/HCTZ (Diovan HCT)	**ACE Inhibitors** ▪ Benazepril +/- HCTZ (Lotensin, Lotensin HCT generic) ▪ Captopril/HCTZ (Capozide, generic) ▪ Enalapril, Enalapril/HCTZ (Vasotec, Vasoretic, generic) ▪ Fosinopril, fosinopril HCTZ (Monopril, Monopril HCT generic) ▪ Moexipril +/- HCTZ (Univasc, Uniretic generic) ▪ Perindopril (Aceon, generic) ▪ Quinapril+/- HCTZ (generic) ▪ Trandolapril (Mavik, generic) **ACE Inhibitor/CCB** ▪ Verapamil SR/trandolapril (Tarka, generic) **ARBs** ▪ Candesartan, Candesartan/HCTZ (Atacand, Atacand HCT) ▪ Eprosartan, Eprosartan/ HCTZ (Teveten, Teveten HCT) ▪ Irbesartan, Irbesartan/HCTZ (Avapro, Avalide) ▪ Olmesartan, Olmesartan/HCTZ (Benicar, Benicar HCT) **RAAs/CCB** ▪ Telmisartan/amlodipine (Twynsta) ▪ Olmesartan/amlodipine (Azor) ▪ Valsartan/amlodipine +/- HCTZ ▪ Valsartan/amlodipine/HCTZ (Exforge HCT) **DRIs** ▪ Aliskiren (Tekturna) ▪ Aliskiren/HCTZ (Tekturna HCT) ▪ Valsartan/aliskiren (Valturna)	**RAAs/CCB** ▪ Olmesartan/amlodipine/ HCTZ (Tribenzor) recommended Feb 2011 **DRIs** ▪ Aliskiren/amlodipine (Tekamlo) recommended Feb 2011	Pending (60 days)	Step therapy (Auto PA)	Note: Tekamlo and Tribenzor are nonformulary and non-step preferred; PA criteria and MN criteria apply **Step-therapy (automated PA)** with the following as the step-preferred drugs: ▪ losartan ±HCTZ ▪ telmisartan ±HCTZ ▪ telmisartan/ amlodipine ▪ valsartan ±HCTZ ▪ valsartan/ amlodipine ▪ valsartan/ amlodipine/HCTZ Note: telmisartan/amlodipine valsartan/amlodipine & valsartan/amlodipine/ HCTZ are step-preferred but not on the BCF

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2011	**Alzheimer's Drugs** Previous review: Nov 2005	• New Drug **Donepezil 23 mg (Aricept 23 mg)**	▪ Donepezil 5 and 10 mg tablets (Aricept, generics)	▪ Galantamine (Razadyne) ▪ Rivastigmine (Exelon) ▪ Memantine (Namenda)	▪ Donepezil 23 mg (Aricept 23 mg) recommended Feb 2011 ▪ Tacrine (Cognex)	Pending 60 days	-	-
Feb 2011	**Newer Antiemetics** Previous review: Nov 2005	• New Drug **Ondansetron soluble film (Zuplenz)**	▪ Promethazine (generics)	▪ Granisetron (generics) ▪ Ondansetron oral tablets (generics)	▪ Ondansetron soluble film (Zuplenz) recommended Feb 2011 ▪ Dolasetron (Anzemet) (Nov 2005) ▪ Granisetron (Sancuso) (May 2009)	Pending 60 days	-	-

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2011	**Self-Monitoring Blood Glucose Test Strips** Previous review Aug 2008	• New test strips **Glucocard 01 Glucocard Vital Embrace NovaMax**	▪ Precision Xtra strips (for Precision Xtra meter)	Recommended Feb 2011 ▪ Glucocard 01test strips (for the Glucocard 01 and Glucocard 01 Mini meters) ▪ Glucocard Vital test strips (for the Glucocard Vital meter) ▪ Embrace test strips (for the Embrace meter) Recommended August 2008 ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters) Recommended Feb 2009 ▪ TRUEtest (for TRUEresult and TRUE2go meters)	Recommended Feb 2011 ▪ NovaMax strips (for Nova Max Plus and Nova Max Link meters) Rec Aug 2008 ▪ OneTouch Ultra 2 strips ▪ TrueTrack strips ▪ Accu-chek Comfort Curve strips ▪ Accu-chek Compact Plus drum ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check. Plus all other store/private label brand strips not included on the UF	Pending 60 days	QL Mail Order: 600 strips/90 days; Retail 200 strips/30 days	-

Appendix D—Table of Abbreviations

5-ASA	5-aminosalicylic acid
5-HT3	serotonin subtype 3
ACE	angiotensin converting enzyme
ARB	angiotensin receptor blocker
BAS	bile acid sequestrants
BCF	Basic Core Formulary
BIA	budget impact analysis
CCB	calcium channel blocker
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFR	Code of Federal Regulations
CHD	coronary heart disease
CMA	cost minimization analysis
CV	cardiovascular
DM	diabetes mellitus
DoD	Department of Defense
DHP	Dihydropyridine
DPP	dipeptidyl-peptidase 4
DRI	direct renin inhibitor
EC	enteric coated
ECF	Extended Core Formulary
EPI	exocrine pancreatic insufficiency
FDA	U.S. Food and Drug Administration
GDH-PQQ	glucose dehydrogenase pyrroloquinolinequinone
GI-1s	Gastrointestinal-1 Drug Class
GLP1RAs	glucagon-like peptide-1 receptor agonists
HCTZ	Hydrochlorothiazide
HDL	high density lipoprotein cholesterol
HbA1c	glycosolated hemoglobin or hemoglobin A1c
IBS	irritable bowel syndrome
IDD-P	Insoluble drug delivery particle formulation of fenofibrate
JNC	Joint National Commission
LDL	low density lipoprotein cholesterol
LIP-2s	Antilipidemic-2s Drug Class
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	Military Treatment Facility
NSAIDs	non-steroidal anti-inflammatory drug class
ODT	orally dissolving tablets
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PEPs	Pancreatic Enzyme Products Drug Class
PORT	Pharmaceutical Outcomes Research Team
QL	quantity limit
RAAs	renin-angiotensin antihypertensives drug class
Rxs	prescriptions
TG	triglyceride
TZDs	thiazolidinediones
VA	Veteran's Affairs

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
November 2010

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on November 16 and 17, 2010, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August Minutes**—George Peach Taylor, Jr., M.D. MPH, Acting Director, approved the minutes for the August 2010 DoD P&T Committee meeting on November 8, 2010.
2. **Reanalysis of Antihemophilic Agents**—The P&T Committee evaluated the relative clinical and cost effectiveness of the Antihemophilic Factors at the February 17–18, 2010, meeting. The minutes were subsequently signed by the Acting Director, TMA, on May 3, 2010. The following Antihemophilic Agents were returned to formulary status on the UF, per execution of the required DoD Retail Refund Pricing Agreement, as signed by George Peach Taylor, Jr., M.D., MPH, Acting Director, on November 8, 2010:
    - Human Factor VIII: Hemofil M
    - Recombinant Factor VIII: Recombinate, Advate
    - Prothrombin Complex Concentrates: Bebulin VH, Feiba VH

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Inhaled Corticosteroid (ICS)/Long-acting Beta Agonist (LABA)—Mometasone/formoterol Oral Inhaler (Dulera)

Relative Clinical Effectiveness—Dulera is a fixed-dose combination (FDC) product containing the ICS mometasone (Asmanex) and the LABA formoterol (Foradil) in an oral metered-dose inhaler (MDI). It represents the third FDA-approved ICS/LABA combination inhaler. The Pulmonary 1 class, which includes the ICS/LABA combinations, was reviewed at the February 2009 P&T Committee meeting. The

clinical evaluation for Dulera included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Dulera is FDA-approved for treating patients older than 12 years with moderate-to-persistent asthma who are not controlled on moderate-to-high dose ICS. Advair is approved for treating asthma in patients older than 4 years, and is also approved for treating chronic obstructive pulmonary (COPD). All three ICS/LABA products (Advair, Symbicort and Dulera) have dose counters.

There are no head-to-head trials between Dulera and the other ICS/LABA combinations inhalers, but clinically relevant differences in efficacy are not expected, if equivalent doses are used.

The product labeling contains the same black box warning as Advair and Symbicort regarding increased risk of death in patients with asthma who receive unopposed LABA therapy.

The mometasone component of Dulera is available on the Basic Core Formulary (BCF) as a single inhaler (Asmanex). For patients who are receiving mometasone and require step-up/step-down therapy to or from a combination ICS/LABA inhaler, maintaining Dulera on the UF allows this population an option to return to their initial ICS.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained) mometasone/formoterol (Dulera) offers no clinically meaningful therapeutic advantage over other ICS/LABA combinations in terms of efficacy, safety, or tolerability. However, it does provide a third ICS/LABA option for the treatment of asthma.

Relative Cost-Effectiveness— Cost-minimization analysis (CMA) was performed to evaluate the cost of mometasone/formoterol (Dulera) in relation to the other currently available ICS/LABAs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) mometasone/formoterol (Dulera) was less costly than the other ICS/LABA combination agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) mometasone/formoterol (Dulera) be designated formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) mometasone/formoterol (Dulera) be excluded from the BCF.

Director, TMA, Decision : ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: QUANTITY LIMTS (QL)***—ICS/LABA combination inhalers on the UF are subject to QLs, which are consistent with the recommended dosing from the product labeling and safety concerns. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) QLs for mometasone/formoterol (Dulera), consistent with the other products in the class: 3 inhalers/90-day supply in the mail order pharmacy and 1 inhaler/30-day supply in the retail point of service.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Newer Sedative Hypnotic Agents (SED-1s)—Doxepin Tablets (Silenor)

Relative Clinical Effectiveness—Silenor is a new low-dose 3mg and 6 mg tablet formulation of doxepin (Sinequan, generics). The product is FDA-approved for treatment of insomnia characterized by difficulty with sleep maintenance. The SED-1s class was reviewed in February 2007. The current BCF/UF drug is zolpidem IR (Ambien, generic). Automated Prior Authorization (PA)/step-therapy applies to this class: a trial of zolpidem immediate release (IR) prior to use of the other drugs in the class is required. Eszopiclone (Lunesta) is designated with formulary status on the UF; the other SED-1s are nonformulary (NF); zolpidem controlled release (Ambien CR), zaleplon (Sonata), and ramelteon (Rozerem). The clinical evaluation for Silenor included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Silenor differs from the other SED-1s because it selectively binds the histamine H1 receptor to reduce wakefulness. It is not a controlled substance; all other agents in the class are classified as schedule IV, except ramelteon (Rozerem).

There are no head-to-head trials with the other SED-1s. Silenor's adverse event profile and discontinuation rate were similar to placebo. There were no reports of aberrant sleep behaviors, increased suicidality, or amnesia that has been noted with the other UF agents. However, a patient medication guide is dispensed with each prescription that details risk of these events.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) doxepin tablets (Silenor) are superior to placebo in the treatment of sleep maintenance insomnia. Silenor's adverse event profile is more favorable that those of formulary agents on the UF. It provides an option for patients with sleep maintenance problems where a controlled substance is not warranted.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of doxepin (Silenor) in relation to the other available newer sedative hypnotics in this drug class. CMA was performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) doxepin tablets (Silenor) was less costly than the other sleep maintenance agents included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) doxepin tablets (Silenor) be designated formulary on UF, with a PA requiring a trial of zolpidem IR for new users.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) doxepin tablets (Silenor) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to doxepin (Silenor). Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:
      (1) The patient has received a prescription for zolpidem IR at any Military Health Service (MHS) pharmacy point of service

(Military Treatment Facilities (MTFs), retail network pharmacies, or home delivery) during the previous 180 days.

b) Manual (paper) PA criteria, if automated criteria are not met:
   (1) The patient has tried zolpidem IR and was unable to tolerate treatment due to adverse effects.
   (2) The patient has tried zolpidem IR and has had an inadequate response.
   (3) The patient has a known contraindication to zolpidem IR.
   (4) The patient requires a nonscheduled agent for sleep maintenance.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. Antilipidemic-1s (LIP-1s)—Pitavastatin (Livalo)

Relative Clinical Effectiveness—Pitavastatin (Livalo) is the seventh statin to reach the U.S. market. At the maximum 4 mg dose, it lowers low-density lipoprotein (LDL) by less than 45%. The statins are classified in the LIP-1s drug class, which were reviewed in May 2010. Automated PA/step-therapy now applies to the LIP-1s; generic statins (simvastatin, pravastatin, lovastatin) or atorvastatin (Lipitor) are the preferred drugs. The clinical evaluation for Livalo included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

There are no published or planned studies evaluating clinical outcomes with pitavastatin (e.g., mortality, cardiovascular (CV) events, acute coronary syndromes, etc.). Short-

term clinical trials lasting less than 12 weeks show efficacy comparable to other low-to-moderate dose statins (those that lower LDL <45%) for lowering LDL and triglyceride (TG), and raising high-density lipoprotein (HDL).

Livalo's safety profile appears similar to the other statins but more long-term safety data is required. Pitavastatin undergoes minimal CYP 450 metabolism and is similar to pravastatin and rosuvastatin, but has a more favorable drug interaction profile than simvastatin. However, pitavastatin is metabolized by the transporter system and has unique drug interactions not seen with the other statins, including contraindications with cyclosporine and reduced dosage requirements with erythromycin.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that pitavastatin (Livalo) does not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and tolerability over other LIP-1s included on the UF, which have evidence for positive effects on CV clinical outcomes.

Relative Cost-Effectiveness—CMA was performed that evaluated the cost of pitavastatin (Livalo) in relation to other available LIP-1s. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) pitavastatin (Livalo) was more costly than all other low-to-moderate LDL-lowering LIP-1s included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) pitavastatin (Livalo) be designated NF on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of pitavastatin (Livalo) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for pitavastatin (Livalo). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—Prior authorization for the LIP-1s requires a trial of a step-preferred drug [simvastatin, lovastatin, lovastatin or atorvastatin (Lipitor)] prior to a non-step preferred LIP-1 [other UF LIP-1s, including rosuvastatin (Crestor), simvastatin/ezetimibe (Vytorin)]. Pitavastatin (Livalo) would be designated as non-step preferred and NF. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to pitavastatin (Livalo).

   a) Automated PA criteria:
      (1) The patient has received a prescription for a preferred agent targeting similar LDL reduction at any MHS pharmacy point of service (MTFs, retail network pharmacies, or home delivery) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:
      (1) The patient has a known contraindication to the preferred LIP-1 drugs.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Narcotic Analgesics—Hydromorphone Hydrochloride (HCl) Extended Release (ER) Tablets (Exalgo)

Relative Clinical Effectiveness—Hydromorphone HCl ER (Exalgo) is a potent opioid agonist that is FDA-approved for the treatment of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. Exalgo is classified as a high-potency single analgesic agent in the Narcotic Analgesics drug class, which was reviewed in February 2007. Exalgo utilizes the osmotic controlled release oral delivery system (OROS) to confer its extended release properties. The delivery mechanism allows for once daily dosing of hydromorphone, which offers a convenient regimen for patients as opposed to the four times a day dosing with the IR formulation. The clinical evaluation for Exalgo included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

There are no direct comparative clinical trials between Exalgo and the other high-potency extended release narcotic analgesics; however, it is unlikely that there are clinically relevant differences in pain relief if equianalgesic doses are administered. Exalgo's safety and tolerability profile is consistent with the known profile of narcotic analgesics. The OROS formulation does not appear to potentiate the known gastrointestinal (GI) effects of hydromorphone (constipation, nausea, and vomiting). Exalgo's hard tablet shell makes it difficult to crush and attempts to dissolve the

particles result in a viscous substance that is potentially fatal if injected. These features, though unproven, may decrease the abuse liability of the drug.

Relative Clinical Effectiveness Conclusion—Despite the fact that there are several other high-potency controlled-release narcotics available on the UF and BCF (many are available in generic formulations), the P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) that Exalgo is the only extended-release hydromorphone product on the market. With the exception that Exalgo provides an option for patients who do not respond to or cannot tolerate other high-potency agents, Exalgo does not offer compelling clinical advantages over the other high-potency long-acting narcotic analgesics included on the UF.

Relative Cost-Effectiveness—CMA was performed that evaluated the cost of hydromorphone HCl ER (Exalgo) in relation to other currently available agents in Narcotic Analgesic drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) hydromorphone HCl ER (Exalgo) was more costly than the other high-potency narcotic analgesics with sustained-release formulations currently on the UF. Exalgo is still a necessary agent because it is the only currently marketed extended-release formulation of hydromorphone HCl in the United States.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (10 for, 6 opposed, 2 abstained, 0 absent) hydromorphone HCl ER (Exalgo) be designated formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 2 opposed, 2 abstained, 0 absent) hydromorphone HCl ER (Exalgo) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

F. Antilipidemic-2s (LIP-2s)—Fenofibric Acid (Fibricor)

Relative Clinical Effectiveness—Fibricor is the second fenofibric acid marketed in the United States; Trilipix, the choline salt of fenofibric acid, was marketed first. The fenofibrates are classified in the LIP-2s drug class, which was reviewed in May 2007. The entire LIP-2s drug class (fenofibrates, omega-3/fish oil, and bile acid sequestrants) is scheduled for review at the February 2011 P&T Committee meeting.

Fibricor is approved for use as monotherapy to reduce TG levels in patients with severe hypertriglyceridemia (>500 mg/dl). In contrast to Trilipix, Fibricor is not FDA-approved for concomitant use with a statin. The fenofibric acid (Fibricor) clinical evaluation included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Fibricor obtained FDA approval via section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using efficacy and safety data submitted from the original fenofibrate nanocrystallized (Tricor) submission. Pharmacokinetic studies comparing Fibricor 105mg with Tricor 145mg demonstrated bioequivalence between the two products. There are no head-to-head clinical trials comparing Fibricor and the other LIP-2s. Fibricor's safety profile reflects that of the other fenofibrate products.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) there is no evidence to suggest Fibricor has a compelling clinical advantage over the fenofibrate products on the UF.

Relative Cost-Effectiveness—CMA was performed that evaluated the cost of fenofibric acid (Fibricor) in relation to other currently available LIP-2s. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) fenofibric acid (Fibricor) was more costly than all other comparators in the fenofibrate subclass of LIP-2s, except for Trilipix or Tricor.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 1 opposed, 1 abstained, 1 absent) fenofibric acid (Fibricor) be designated NF on the UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of fenofibric acid (Fibricor) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) MN criteria for fenofibric acid (Fibricor). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF

decision. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

G. Contraceptives—Estradiol Valerate/Dienogest (Natazia)

Relative Clinical Effectiveness—Natazia is a combination oral contraceptive containing a new dosage form of estradiol valerate (which was previously only available in an injectable form) and a new progestin (dienogest). It utilizes a 4-phasic active drug regimen with 2 hormone-free days.

Estradiol valerate/dienogest is solely indicated for the prevention of pregnancy. It is included in the Contraceptive Agents drug class, which was reviewed in May 2006. The clinical evaluation for estradiol valerate/dienogest (Natazia) included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

A head-to-head comparison between Natazia and 20 mcg ethinyl estradiol/100 mg levonorgestrel (Lessina, Sronyx equivalent) found significantly fewer days of withdrawal (scheduled) bleeding with Natazia but a similar incidence of intracyclic (unscheduled) bleeding, due to the shorter number of hormone-free days (2 with Natazia versus 7 with the comparator). Spotting or breakthrough bleeding is still common, especially when therapy is first started.

The adverse event profile for Natazia is similar to that of other oral contraceptives. The patient instructions for missed doses are significantly more complicated than those for other oral contraceptives. The purported benefits of 4-phasic contraceptive regimens remain to be established and Natazia's long-term safety remains unknown.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 1 abstained, 1 absent) estradiol valerate/dienogest (Natazia) does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other oral contraceptives on the UF.

Relative Cost-Effectiveness— CMA was performed to evaluate the cost of estradiol valerate/dienogest (Natazia) in the Contraceptive Agents drug class. Information

considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) estradiol valerate/dienogest (Natazia) was more costly than all other contraceptive agents on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) estradiol valerate/dienogest (Natazia) be designated NF on the UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of estradiol valearate/dienogest (Natazia) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) MN criteria for estradiol valerate/dienogest (Natazia). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF

decision. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved □ Disapproved

Approved, but modified as follows:

IV. UF DRUG CLASS REVIEWS

A. Non-Insulin Diabetes Drugs

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the drugs in the Non-insulin Diabetes drug class. The clinical review for the non-insulin diabetes drugs included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The class is comprised of the following 8 subclasses: dipeptidyl-peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP1RAs), biguanides (metformin), thiazolidinediones (TZDs), sulfonylureas (SU), meglitinides, alpha-glucosidase inhibitors (AGIs), and amylin agonists (pramlintide; Symlin), and their FDC products with metformin or SU. The Non-insulin Diabetes drug class as a whole has not previously been reviewed.

The Non-insulin Diabetes drug class is ranked in the top 5 most costly MHS drug classes, with expenditures exceeding $311 million annually. For the individual subclasses, Fiscal Year 2010 expenditures for the DPP-4 inhibitors were approximately $124 million, followed by the TZDs ($108 million), GLP1RAs ($28 million), biguanides ($23 million), SUs ($15 million), meglitinides ($9 million), amlyin agonists ($3 million), and AGIs ($800,000).

In terms of MHS utilization, the biguanides are the most utilized (approximately 225,000 30-day equivalent prescriptions (Rxs) dispensed monthly), followed by the SUs (160,000 30-day equivalent Rxs), TZDs (100,000 30-day equivalent Rxs), and DPP-4 inhibitors (60,000 30-day equivalent Rxs); the GLP1RAs, meglitinides, AGIs, and amylin agonists each account for less than 10,000 30-day equivalent Rxs dispensed monthly.

American Diabetes Association (ADA) Guidelines (Diabetes Care, 2009, 32:193-203) recommend metformin, in addition to lifestyle modification, as first-line therapy for Type 2 Diabetes Mellitus (T2DM) and is considered in tier 1 (well-validated therapy). SUs or basal insulin are recommended next in the hierarchy (second-line, tier one).

Tier two or less well-validated therapies include the TZDs and GLP1RAs. No recommendation is made for DPP-4 inhibitors, but the algorithm is updated annually in January.

A request for MHS providers' opinions solicited over 440 responses. When asked which subclass was most appropriate for first-line therapy for T2DM, over 98% of the responders selected metformin, followed by the SUs (62% of responders), TZDs (39%), DPP-4 inhibitors (36%), and GLP1RAs (23%).

Based on recommendations from the current ADA guidelines (metformin first-line, followed by SUs as tier one, well-validated therapies for T2DM) and the MHS providers' responses, an automated PA/step-therapy was considered for the Non-insulin Diabetes drug class, which would require a trial of metformin or a SU prior to using another Non-insulin Diabetes subclass. Step-therapy was also considered for the TZDs, GLP1RAs, and DPP-4 inhibitors within each subclass (e.g., requiring a trial of a step-preferred drug before using the other drugs in the subclass).

DoD Pharmacy Outcomes Research Team (PORT) Analysis: MHS Patterns of Use of Diabetes Drugs—The PORT analyzed data for new users of insulin and non-insulin diabetes drugs. Overall, 619,993 unique DoD beneficiaries received one or more Rxs for a diabetes medication (including insulin) during the one-year period from July 1, 2009–June 30, 2010.

The breakdown of classes is:

- 68% metformin/metformin FDC products
- 36% SU/SU FDC products
- 30% insulin
- 22% TZD/TZD FDC products
- 15% DPP-4 inhibitors
- 4% GLP1RAs
- 3% meglitinides, AGIs or pramlintide

Approximately 102,000 new users of diabetes medications are expected annually across all points of service in the MHS. For the DPP-4 inhibitors, an estimated 35,364 new users are expected each year; 17% of the new users may start first-line on a DPP-4 inhibitor, and are not expected to have had a prior prescription for metformin or a SU. There are 12,024 estimated new users for the GLP1RAs; 10% are anticipated to have no prior prescription for metformin or a SU.

Background Relative Cost Effectiveness—Cost-effectiveness analysis (CEA) was conducted to provide an overall assessment of the relative cost-effectiveness among the following subclasses used for second-line therapy (when added to metformin): AGIs,

basal insulins, DPP-4 inhibitors, GLP1RAs, meglitinides, SUs, and TZDs. The Basal Insulin drug class was reviewed in February 2010 but is included in the CEA due to its inclusion in the ADA guidelines.

Relative Cost Effectiveness Conclusion—For subclasses added as second-line therapy to metformin, the SU subclass were considered to be dominant (e.g., providing the largest reduction in HbA1c at the lowest cost) in terms of cost per HbA1c reduction, followed by the basal insulins. GLP1RAs and TZDs were more expensive therapies than the SUs with relatively little difference in HbA1c efficacy. The DPP-4 inhibitors were similar in efficacy to the SUs but were less cost effective.

B. Non-insulin Diabetes Drugs—Biguanides

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Biguanides subclass. Metformin is the only biguanide drug currently on the market. The Biguanides subclass has not previously been reviewed; all the drugs are currently designated with formulary status on the UF. The BCF includes all strengths of generic metformin IR and ER; BCF metformin products were selected prior to implementation of the UF Rule in 2005. The clinical review focused on use of metformin for T2DM (non-DM uses were not considered) and included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The individual metformin formulations are:

- **Metformin IR:** 500 mg, 850 mg, 1000 mg tablets (Glucophage, generics); 500 mg/5 ml liquid (Riomet)
- **Metformin ER:** 500 mg, 750 mg (Glucophage XL, generics); 500 mg, 1000 mg (Fortamet); and 500 mg, 1000 mg (Glumetza)

Metformin IR has the highest utilization, with over 200,000 30-day equivalent Rxs dispensed monthly in the MHS, followed by generic metformin ER products (40,000 30-day equivalent Rxs dispensed monthly). There were <1,000 30-day equivalent Rxs dispensed monthly for the branded metformin ER products Fortamet and Glumetza.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the Biguanides subclass:

1. The ADA guidelines recommend metformin as the first-line, tier one (well-validated therapy) for the treatment of T2DM.

2. When used as monotherapy, metformin decreases HbA1c by 1.5%–2%.

3. With regard to efficacy, the results of one large prospective sub-study of the United Kingdom Prospective Diabetes Study (UKPDS) reported beneficial effects of metformin on improving clinical outcomes, including a risk reduction for diabetes-related death and all-cause mortality, when compared to dietary modification.

4. There is no evidence to suggest that differences in the ER formulations of Glumetza and Fortamet confer clinically relevant benefits in efficacy or safety when compared to the generic metformin ER preparations.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the Biguanides subclass. Metformin and metformin combination products were evaluated with the parent compound (e.g., Janumet (sitagliptan/metformin) was evaluated with the DPP-4s subclass.) CMAs were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) all generic formulations of metformin and the branded drug Riomet were more cost-effective than Fortamet and Glumetza.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 1 opposed, 1 abstained, 0 absent):

   a) metformin IR (500 mg, 850 mg,1000 mg), metformin ER (500 mg, 750 mg), and Riomet (500 mg/5 ml) remain formulary on the UF;

   b) Fortamet (500mg, 1000 mg) and Glumetza (500 mg, 1000 mg) be designated NF on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) metformin IR (500 mg, 850 mg, 1000 mg), and metformin ER (500 mg, 750 mg) remain on the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of Fortamet and Glumetza and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) MN criteria for Fortamet and Glumetza. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the committee's recommendation, the effective date is April 13,, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Non-insulin Diabetes Drugs—SUs

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the SUs subclass. The SUs have not previously been reviewed; all the drugs are currently designated with formulary status on the UF. The BCF includes glipizide (Glucotrol, generics), glyburide (Diabeta, Micronase, generics), and glyburide micronized (Glynase Pres Tab, generics). BCF SU products were selected prior to implementation of the UF Rule in 2005. All the SU products are available in generic formulations. In the MHS, glipizide is the highest utilized sulfonylurea agent. The clinical review for the SUs included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The individual SUs agents are:

- **First generation :** chlorpropamide (Diabinese, generic)
- **Second generation:** glimepiride (Amaryl, generic), glipizide (Glucotrol, generic), glipizide ER (Glucotrol XL, generic), glyburide (Diabeta, Micronase, generic), glyburide, micronized (Glynase Press Tab, generic)
- **Combination products:** glipizide/metformin (Metaglip, generic), glyburide/metformin (Glucovance, generic)

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the SUs:

1. The ADA guidelines recommend SUs as the second-line of tier one, (well-validated therapies) for the treatment of T2DM.
2. The SUs decrease HbA1c 1.5% to 2% when used as monotherapy.
3. In a UKPDS sub-study, patients receiving a SU or insulin had a lower risk of developing any diabetes-related endpoint and microvascular endpoints than patients receiving dietary modification alone. Diabetes-related mortality and all-cause mortality did not differ between the two groups.
4. For adverse effects, the SUs are well known to cause hypoglycemia and weight gain.
5. With regard to renal dysfunction, glipizide may be used in patients who have creatinine clearance <50 mL/min if the dose is reduced.
6. With regard to special populations, glyburide crosses the placenta in minimal amounts. In one retrospective review of more than 500 women

with gestational diabetes, glyburide treatment resulted in achievement of target HbA1c.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the SUs subclass. SUs and SU combination products were evaluated with the parent compound (e.g., Duetact (pioglitazone/glimepiride) was evaluated with the TZDs subclass). Chlorpropamide was not evaluated due to its extremely low utilization in the MHS. CMAs were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) all agents in the SUs subclass were cost-effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following remain formulary on the UF:

    a) chlorpropamide (Diabinese, generic); glimepiride (Amaryl, generic); glipizide (Glucotrol, generic); glipizide ER (Glucotrol XL, generic); glyburide (Diabeta, Micronase, generic); glyburide micronized (Glynase Press Tab, generic); glipizide/metformin (Metaglip, generic); and glyburide/metformin (Glucovance, generic)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following remain on the BCF:

a) glipizide (Glucotrol, generic); glyburide (Diabeta, Micronase, generic); and glyburide micronized (Glynase Press Tab, generic)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Non-insulin Diabetes Drugs—DPP-4 Inhibitors

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the DPP-4 inhibitors subclass. The DPP-4 inhibitors subclass includes sitagliptin (Januvia), sitagliptin/metformin (Janumet), and saxagliptin (Onglyza). A FDC product saxagliptin/metformin ER (Kombiglyze XR) recently received FDA approval and will be reviewed an upcoming meeting. The DPP-4 inhibitors have not previously been reviewed. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following clinical effectiveness conclusions for the DPP-4 inhibitors subclass:

1. The ADA guidelines do not mention DPP-4 inhibitors. However, the DPP-4 inhibitors may be mentioned when the guidelines are updated next year, given wider clinical use and concerns regarding the TZD safety profile.
2. There are no completed long-term studies assessing CV outcomes, although 2 studies are under way; the TECOS trial with sitagliptin and the SAVOR-TIMI 53 trial with saxagliptin. Results are expected in 2014–2015.
3. Monotherapy with sitagliptin 100mg daily reduced HbA1c on average by 0.6%–0.79% (mean difference from placebo); whereas, saxagliptin monotherapy reduced HbA1c approximately 0.4%–0.7%. Adding sitagliptin to metformin or pioglitazone (Actos) reduced HbA1c 0.5%–0.9%. The FDC sitagliptin 50mg plus metformin 1000mg (Janumet) given twice daily reduced HbA1c by 1.9% from baseline.

4. There is one published head-to-head non-inferiority trial evaluating glycemic control between the two DPP-4 inhibitors when added to stable metformin therapy. Sitagliptin lowered HbA1c by approximately 0.1% more from baseline than saxagliptin. Saxagliptin was considered non-inferior to sitagliptin. While statistical significance was achieved, the difference between the two agents is not clinically significant.
5. When used as monotherapy or when combined with metformin, DPP-4 inhibitors may provide weight loss; typically less than -0.7 kg from baseline with sitagliptin and metformin and -1.8 kg from baseline with saxagliptin and metformin. When the DPP-4s are combined with SUs or TZDs, weight gain may occur, which is a known adverse effect of the SUs and TZDs subclasses. Therefore, DPP-4 inhibitors are generally considered to be weight-neutral.
6. Effects on lipid parameters were assessed in some but not all studies with the DPP-4 inhibitors. DPP-4 inhibitors are generally considered to have neutral effects on lipids.
7. In terms of commonly reported adverse events, there are no clinically relevant differences between sitagliptin and saxagliptin. Drug interaction profiles are also similar between agents.
8. In terms of serious adverse events, 88 cases of acute pancreatitis have been reported to the FDA as of September 2009. The majority of cases occurred with sitagliptin, but sitagliptin has a longer marketing history than saxagliptin.
9. Results from a request for MHS providers' input showed the majority of responders stated at least one DPP-4 inhibitor was necessary on the UF. Providers would be willing to use either sitagliptin or saxagliptin, but acknowledged more familiarity with sitagliptin.
10. There is a high degree of therapeutic interchangeability between sitagliptin and saxagliptin.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the DPP-4 inhibitors. CMAs and budget impact analyses (BIAs) were performed based on findings that there were no clinically relevant differences in efficacy, safety, tolerability, and other factors among the DPP-4 inhibitors. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) the following:

- BIA was used to assess the potential impact of cost scenarios where selected DPP-4 inhibitors and DPP-4 inhibitor FDCs were designated as formulary or NF on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered. BIA results for the DPP-4 inhibitors subclass showed that all investigated scenarios resulted in lower cost estimates than current MHS expenditures. Sensitivity analysis results supported the above conclusion.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) sitagliptin (Januvia), sitagliptin/metformin (Janumet), and saxagliptin (Onglyza) remain formulary on the UF. Prior authorization/step-therapy for the DPP-4 inhibitors would require a trial of metformin or SUs for new patients.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 1 opposed, 1 abstained, 1 absent) sitagliptin (Januvia) and sitagliptin/ metformin (Janumet) be added to the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

      (2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, or Onglyza) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual PA criteria, if automated criteria are not met:

      (1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.

      (2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

      (3) The patient has a contraindication to both metformin and a SU.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. Non-insulin Diabetes Drugs—GLP1RAs

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the GLP1RAs subclass. The GLP1RAs subclass includes exenatide (Byetta) injection and liraglutide (Victoza) injection. The GLP1RAs have not previously been reviewed. Prior authorization currently applies to the class, which excludes off-label use of the drugs for obesity in patients who do not have DM. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following clinical effectiveness conclusions for the GLP1RAs:

1. The ADA guidelines for T2DM place GLP1RAs in tier 2, (less well-validated therapy) after therapeutic lifestyle modification plus metformin.
2. Both exenatide and liraglutide are indicated for use in patients with T2DM as monotherapy, and in combination with metformin, SUs, or TZDs. Off-label uses of the GLP1RAs include weight loss in patients without DM; weight loss is not a benefit covered by TRICARE.
3. Exenatide is dosed twice daily 30–60 minutes prior to meals whereas liraglutide is dosed once daily without regard to meals. The titration schedule and maximum doses differ between the two drugs.
4. There are no long-term studies assessing CV outcomes. However, two trials are underway: the EXSCEL trial (using an investigational formulation of exenatide dosed once weekly), and the LEADER trial (with liraglutide). Results are expected in 2016–2017.
5. GLP1RAs offer another option for add-on therapy when oral agents (e.g., metformin, SUs, TZDs) no longer provide adequate glycemic control. When combined with metformin, SU, or both metformin and SU, exenatide 10mcg twice daily lowered HbA1c 0.77%–0.86% from

baseline. Liraglutide 1.8mg once daily, when combined with metformin and SU, lowered HbA1c 1.3% from baseline.

6. Both exenatide and liraglutide improve fasting plasma glucose (FPG) and postprandial glucose (PPG) concentrations; however, liraglutide has a greater effect on lowering FPG than PPG due to its longer duration of action. In contrast, exenatide has a greater effect on PPG than FPG.
7. Exenatide and liraglutide have been compared to insulin glargine (Lantus); both trials were non-inferiority in design. GLP1RAs offer no clinically significant reduction in HbA1c compared to basal insulin.
8. LEAD-6 is the only head-to-head trial between exenatide and liraglutide. Using the maximum doses of each agent, liraglutide showed a greater decrease in HbA1c compared to exenatide (1.16% versus 0.87%), respectively. While the difference of 0.29% was statistically significant, it was not clinically significant. Limitations to the study included the open-label and non-inferiority study design and sponsorship by the manufacturer of liraglutide.
9. The relationship between weight loss and HbA1C was assessed in the LEAD-6 trial. The difference in HbA1C reduction between patients with and without weight loss was not statistically significant. Patients using a GLP1RA as monotherapy, or in combination with metformin, can expect a 2 kg to 3 kg weight loss.
10. Lipid parameters improved or remained neutral in the exenatide and liraglutide trials; changes in the lipid levels were not statistically significant.
11. There are no clinically relevant differences among the GLP1RAs in common adverse events (nausea and hypoglycemia) and drug interactions.
12. Serious adverse events reported with the GLP1RAs include altered renal function with exenatide, and rare pancreatitis with both exenatide and liraglutide. Both agents may cause formation of antibodies to the GLP1RA. Liraglutide has a black box warning for risk of developing thyroid C-cell tumors and is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.
13. Both agents are available in prefilled pen devices. Exenatide requires two different pens to titrate patients to the target 10mcg twice daily

dose. Conversely, all three doses of liraglutide are available in one dial-a-dose pen.

14. Results from a request for MHS providers' input showed that 49% of responders replied a GLP1RA was required on the UF, 21% were undecided, and 30% replied a GLP1RA was not required on the UF. Providers had little to no experience with liraglutide; however, 63% were willing to prescribe the drug if efficacy and cost were similar to exenatide.
15. With the exception that liraglutide offers patient convenience of a decreased dosing frequency compared to exenatide (daily versus twice daily, respectively), and that liraglutide targets FPG while exenatide targets PPG, there is a high degree of therapeutic interchangeability between the two products in terms of glycemic control. There is a lower degree of therapeutic interchangeability between the two products in terms of serious adverse events of endocrine system tumors.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the GLP1RAs subclass. CMAs and BIAs were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 1 abstained, 1 absent) the following:

- BIA was used to assess the potential impact of cost scenarios where selected GLP1RAs were designated as formulary or NF on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.

- Victoza (liraglutide) pens are less costly than Byetta (exenatide) pens when comparing price per pen. However, Victoza (liraglutide) patients require 2 or 3 pens per 30 days of therapy. Byetta (exenatide) patients only require 1 pen for 30 days of therapy. From a perspective examining cost-per-day of therapy, Byetta (exenatide) is significantly less costly than Victoza (liraglutide). The scenario where Byetta (exenatide) was step-preferred on the UF while Victoza (liraglutide) was non-preferred and remained on the UF was determined to be the most cost-effective scenario. A sensitivity analysis was performed on the percentage of new users receiving a Victoza (liraglutide) prescription.

Sensitivity analysis results showed that market share gains by Victoza (liraglutide) will result in additional costs to the MHS.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) exenatide (Byetta) be designated formulary on the UF (step-preferred), and liraglutide (Victoza) be designated as formulary on the UF (non-preferred). Prior authorization for the GLP1RAs would require a trial of metformin or SUs for new patients. Exenatide (Byetta) was designated as the preferred drug within the subclass; a trial of exenatide (Byetta) would be required prior to liraglutide (Victoza) for new patients.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 1 opposed, 2 abstained, 1 absent) excluding exenatide (Byetta) and liraglutide (Victoza) from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended the following PA criteria should apply to the GLP1RAs. The prior PA criteria for the GLP1RAs would be replaced by the new criteria. Coverage would be approved if the patient met the following criteria:

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria would apply to both exenatide (Byetta) and liraglutide (Victoza):

a) Automated PA criteria:

(1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

AND

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria would apply to liraglutide (Victoza):

b) Automated PA criteria:

(1) The patient has received a prescription for exenatide (Byetta) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

c) Manual PA criteria, if automated criteria are not met:

The following would apply to exenatide (Byetta) and liraglutide (Victoza):

(1) The patient has a confirmed diagnosis of T2DM.

(2) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.

(3) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

(4) The patient has a contraindication to both metformin and a SU.

In addition to the above criteria regarding metformin and SU, the following PA criteria would apply specifically to liraglutide (Victoza):

(1) The patient has a contraindication to exenatide (Byetta).

(2) The patient has had inadequate response to exenatide (Byetta).

(3) The patient has experienced an adverse event with exenatide (Byetta), which is not expected to occur with liraglutide (Victoza).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒Approved □ Disapproved

Approved, but modified as follows:

F. Non-insulin Diabetes Drugs—TZDs

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the TZDs subclass. The subclass is comprised of rosiglitazone and pioglitazone, and FDC products with metformin or SU. The individual TZDs are:

- **Rosiglitazone drugs:** rosiglitazone (Avandia), rosiglitazone/metformin (Avandamet), rosiglitazone/glimepiride (Avandaryl)
- **Pioglitazone drugs:** pioglitazone (Actos), pioglitazone/metformin (Actoplus Met), pioglitazone/metformin ER (Actoplus Met XR), pioglitazone/glimepiride (Duetact)

None of the TZDs are available in generic formulations; the patent for pioglitazone is expected to expire in 2012.

The TZDs were reviewed previously for UF placement. Currently all the TZDs are designated formulary on the UF and there are no BCF drugs. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) the following clinical effectiveness conclusions for the TZDs subclass:

1. ADA guidelines list pioglitazone (but not rosiglitazone) as a step 2, tier 2, (less well-validated) therapy for the treatment of T2DM.
2. Based on meta-analyses and head-to-head trials, rosiglitazone and pioglitazone at maximal doses reduce HbA1c by 0.6% to 1.6%. The differences between the two drugs for HbA1C reduction are not clinically relevant, when used as monotherapy or when combined with metformin, SUs, or insulin.
3. Outcomes studies are available with the TZDs. Pioglitazone in the PROactive trial resulted in a statistically significant reduction in the composite endpoint, including all-cause mortality, non-fatal myocardial infarction (MI) (including silent MI), stroke, and above the knee major leg amputation. In contrast, there is no direct evidence that rosiglitazone prevents vascular events in patients with T2DM.
4. The TZDs differ in their effects on the lipid profile. Pioglitazone has a less unfavorable effect on lipid parameters than rosiglitazone.
5. Safety and tolerability profiles are similar between rosiglitazone and pioglitazone in terms of incidence of heart failure, weight gain, edema, and hypoglycemia.
6. Rosiglitazone is associated with an increase in adverse CV events that is not seen with pioglitazone, based on results of meta-analyses, an open label, non-inferiority trial (RECORD), and a retrospective study using the Medicare database (Graham, JAMA 2010). The rosiglitazone product labeling includes a black box warning regarding increased risk of MI.
7. The FDA has allowed rosiglitazone to remain on the U.S. market, but the manufacturer must develop a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS) with measures limiting rosiglitazone use to patients unable to attain glycemic control with other drugs. An ongoing head-to-head trial (TIDE) comparing CV events between rosiglitazone and pioglitazone has been halted. In Europe, rosiglitazone has been removed from the market.
8. The FDA released a safety communication regarding a potential increase in risk of bladder cancer with pioglitazone. Studies are ongoing to further assess this risk.
9. The DoD PORT analyzed the effects of discontinuing TZDs and switching between pioglitazone and rosiglitazone. Observations from the analysis suggest that TZDs were discontinued, rather than substituted with another non-insulin diabetes drug subclass or insulin. Of the 24,683 patients total who received rosiglitazone in the analysis timeframe, 73% of these patients continued with

rosiglitazone, 8% switched to pioglitazone, 13% received (or continued to receive) other diabetes medications, but not TZDs, and 6% did not fill a Rx for any diabetes medication (including insulin). Changes in utilization patterns are likely to accelerate with implementation of the REMS program for rosiglitazone.

10. The PORT also commented on trends that show a sharp decrease in use of rosiglitazone and an overall decrease in TZD use. New users of rosiglitazone fell from 274 during June 2010 to 34 during October 2010, MHS-wide. New users of pioglitazone also decreased month-by-month, with 2,202 new users in June 2010 compared to 1,372 during October 2010.
11. Results from a request for MHS providers' input showed that 69% of responders would prefer pioglitazone over rosiglitazone; 75% of the responders stated a TZD/metformin FDC product was not required on the UF.
12. In terms of glycemic control, there is a high degree of therapeutic interchangeability between rosiglitazone and pioglitazone. However, there is a lower degree of therapeutic interchangeability with regard to safety profiles.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the TZDs subclass. CMAs were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 1 abstained, 1 absent) rosiglitazone and rosiglitazone FDCs [rosiglitazone (Avandia), rosiglitazone/ metformin (Avandamet), and rosiglitazone/glimepiride (Avandaryl)] are more cost-effective than pioglitazone and pioglitazone FDCs [pioglitazone (Actos), pioglitazone/metformin (Actoplus Met, Actoplus Met RX), and pioglitazone/glimepiride (Avandaryl)]. Additionally, increased safety concerns for rosiglitazone and rosiglitazone FDCs outweigh their apparent cost efficiency.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent):

a) pioglitazone (Actos), pioglitazone/metformin (Actoplus Met, Actoplus Met RX), and pioglitazone/glimepiride (Duetact) remain designated formulary on the UF;

b) rosiglitazone (Avandia), rosiglitazone/ metformin (Avandamet), and rosiglitazone/glimepiride (Avandaryl) be designated NF on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) pioglitazone, pioglitazone FDC products, rosiglitazone, and rosiglitazone FDC products be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of rosiglitazone and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) MN criteria for rosiglitazone (Avandia), rosiglitazone/ metformin (Avandamet), and rosiglitazone/glimepiride (Avandaryl). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria should apply to the TZDs subclass. Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for metformin or SU s at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

      (2) The patient has received a prescription for a TZD at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual PA criteria, if automated criteria are not met:

      (1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.

      (2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

      (3) The patient has a contraindication to metformin and SUs.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

5. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision. Based on the committee's recommendation, the effective date is April 13, 2011.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

G. Non-insulin Diabetes Drugs—Meglitinides

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Meglitinides subclass. The subclass includes nateglinide (Starlix, generic), repaglinide (Prandin), and the FDC product repaglinide/metformin (Prandimet). The Meglitinides subclass has not previously been reviewed. Repaglinide has the highest MHS utilization in this subclass. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the Meglitinides subclass:

1. The ADA guidelines consider the meglitinides as "other therapies," and the subclass is not considered in the tier one (well-validated) or tier two (less well-validated) therapies. Joint guidelines from the DoD/Veterans Affairs (VA) list the meglitinides as alternative agents, which may be used after therapy with metformin or the SUs.
2. Average HbA1c reductions for the subclass range from 0.1% to 2.1% with repaglinide (Prandin), 0.2% to 0.6% with nateglinide, and 1.4% with repaglinide/metformin (Prandimet).
3. In a systematic review by the Cochrane group, repaglinide and nateglinide both reduced HBA1c >0.5% versus placebo (range for nateglinide 0.2%–0.6%; range for repaglinide 0.1%–2.1%).
4. In terms of adverse events, nateglinide and repaglinide can cause hypoglycemia; assistance is rarely required. In the Cochrane systematic review, weight gain ranging from 0.7 kg to 2.1 kg occurred with both agents.
5. In terms of efficacy or safety/tolerability, there were no clinically relevant differences between nateglinide and repaglinide overall.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the Meglitinides subclass. CMAs were performed. Information

considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that all meglitinides in this subclass were cost-effective.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 2 absent) nateglinide (Starlix, generic), repaglinide (Prandin), and repaglinide/metformin (Prandimet) be designated formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 2 absent) nateglinide (Starlix, generic), repaglinide (Prandin), and repaglinide/metformin (Prandimet) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

H. Non-insulin Diabetes Drugs—AGIs

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the AGIs subclass. The subclass is comprised of acarbose (Precose, generics) and miglitol (Glyset). The AGIs have not previously been reviewed. The subclass has very low utilization in the MHS. The clinical review included, but was not

limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the AGIs subclass:

1. The ADA guidelines consider the AGIs as "other therapies," and the subclass is not considered in the tier one (well-validated) or tier two (less well-validated) therapies. Joint guidelines from the DoD/VA list the AGIs as alternative agents, which may be used after therapy with metformin or the SUs.
2. The AGIs reduce HbA1c by less than 1%; acarbose reduces HbA1c by 0.77% and miglitol reduces HbA1c by 0.68%. A decrease in HbA1c by 0.5% is considered clinically relevant.
3. In terms of efficacy or safety/tolerability, there were no clinically relevant differences between acarbose and miglitol overall. The significant GI adverse effects caused by AGIs, the requirement for multiple-daily dosing, and the minimal reduction in HbA1c limit the clinical usefulness of this subclass when compared to the other non-insulin diabetes drug subclasses.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the AGIs subclass. CMAs were performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) acarbose (Precose, generics) and miglitol (Glyset) were cost-effective for the subset of patients who could tolerate the frequent GI side effects and multidose regimens required by these agents.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 1 opposed, 1 abstained, 0 absent) acarbose (Precose, generics) and miglitol (Glyset) be designated formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (17 for, 0 opposed, 1 abstained, 0 absent) acarbose (Precose, generics) and miglitol (Glyset) be excluded from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

I. Non-insulin Diabetes Drugs—Amylin Agonists (Pramlintide)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Amylin Agonists subclass. Pramlintide (Symlin) injection is the only amylin agonist currently on the market. Pramlintide has not previously been reviewed; it is currently designated with formulary status on the UF. Due to safety concerns, a PA was implemented in 2005 to ensure appropriate dosing of pramlintide, which is consistent with the product labeling. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following clinical effectiveness conclusions for the Amylin Agonists subclass:

1. The ADA guidelines for T2DM do not mention the place in therapy for pramlintide.
2. Pramlintide is indicated as adjunctive therapy for the treatment of Type 1 diabetes (T1DM) and T2DM when patients are inadequately controlled on intensive insulin regimens (e.g., bolus insulin doses with meals). Off-label uses of pramlintide include weight loss in patients without DM; weight loss is not a benefit covered by TRICARE.

3. Patients with T1DM showed an average decrease in HbA1c from baseline ranging from -0.1% to -0.39% with pramlintide compared to -0.12% to +0.09% with placebo. In patients withT2DM, the average change in HbA1c ranged from -0.3% to -0.62% with pramlintide versus -0.15% to -0.25% with placebo.
4. There are no outcomes studies with pramlintide.
5. Pramlintide causes weight loss. Mean weight loss with pramlintide ranged from -1.0 kg to -2.3 kg in patients with T1DM compared to a weight gain of 0.3 kg with placebo.
6. Pramlintide is available in multidose vials and a prefilled pen device. Because the product is dosed in mcg, dosing errors are a concern when vials are used but drawn up in insulin syringes marked with units. The prefilled pen device includes a dial-a-dose feature which decreases the risk of dosing errors.
7. Results from a request for providers' input showed over 90% of respondents do not prescribe pramlintide.
8. Pramlintide is efficacious in lowering HbA1c and improving glycemic control, and patients can expect a 1 kg to 2 kg weight loss. However, its clinical utility is limited because it cannot be mixed with insulin, patients require multiple injections of insulin and pramlintide at separate times, there is an increased risk of dosing errors when vials are used, and insulin doses must be decreased by 50% on initiation of therapy to reduce the risk of hypoglycemia.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the Amylin Agonists subclass. A CMA was performed. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) that pramlintide is cost-effective as an adjunct treatment in T1DM and T2DM patients who cannot achieve desired glucose control despite optimal insulin.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16

for, 0 opposed, 1 abstained, 1 absent) pramlintide (Symlin) injection remain designated as formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (16 for, 0 opposed, 1 abstained, 1 absent) excluding pramlintide (Symlin) from the BCF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following PA criteria should apply to the pramlintide (Symlin). Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for bolus insulin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   The current PA for pramlintide (Symlin) does not exclude use in obese patients who do not have DM. The P&T Committee recommended adding the following to the existing manual PA:

   b) Manual PA criteria, if automated criteria are not met:

(1) The patient has a confirmed diagnosis of T1DM or T2DM.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION: PA IMPLEMENTATION PERIOD***—The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. BASIC CORE FORMULARY ISSUES—FENOFIBRATE MELTDOSE (FENOGLIDE) BCF DELETION

The LIP-2s drug class was previously reviewed for UF placement in May 2007. At that time, fenofibrate insoluble drug delivery micro-particle (Triglide) was added to the BCF. In June 2008, fenofibrate meltdose (Fenoglide) replaced Triglide on the BCF, and a $3.00 co-pay was implemented. Changes in licensing and manufacturing agreements have disrupted the availability of Fenoglide, and MTFs are unable to obtain the product. Due to the back order situation, the P&T Committee recommended removing fenofibrate meltdose (Fenoglide) from the BCF. The LIP-2 drug class will be re-reviewed at an upcoming meeting.

1. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to:
   a) remove Fenoglide from the BCF;
   b) maintain Fenoglide with formulary status on the UF;
   c) raise the co-pay from $3.00 to $9.00; and
   d) notify beneficiaries of the change in formulary status.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Based on the manufacturer's (Shore Therapeutics) refusal to sign a Master Agreement with the VA and participate in the drug discount program required by 38 U.S.C. 8126, and on the manufacturer's voluntary removal of Fenoglide from the TRICARE Pharmacy Benefits Program on November 24, 2010, Fenoglide is no longer covered by TRICARE.

VI. UTILIZATION MANAGEMENT—PA

A. Fingolimod (Gilenya)—PA: Fingolimod is an oral disease-modifying agent for multiple sclerosis (MS). It is FDA-approved for treating patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability. Fingolimod is the first oral agent marketed for the treatment of relapsing MS and its cost per month of therapy is considerably more than that of injectable interferon agents on the UF. The fingolimod product labeling states it is not approved for concurrent use with the injectable interferons or glatiramer injection (Copaxone).

1. ***COMMITTEE ACTION: PA CRITERIA AND IMPLEMENTATION***—To ensure the appropriate use of fingolimod is consistent with the product labeling, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) implementing a PA, which will allow use of fingolimod (Gilenya) in patients who met the following criteria:

    a) a documented diagnosis for relapsing forms of MS;

    b) no current use of interferon alpha/beta or Copaxone;

    The fingolimod PA becomes effective the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

    Director, TMA, Decision: ☒ Approved ☐ Disapproved

    Approved, but modified as follows:

B. Fentanyl Citrate—Expansion of PA: In August 2007, an automated PA was implemented for transdermal fentanyl to ensure patients are not opioid-naïve. The dispensing process is stopped with a warning if there is no previous prescription for a high-potency opioid in the pharmacy profile within the past 60 days. Pharmacists at all points of service have the ability to override the system warning after determining that the patient could be presumed to be opioid-tolerant. Fentanyl transmucosal tablets (Fentora) and lozenges (Actiq, generic) were added to the automated PA in May 2009.

The P&T Committee discussed expanding the fentanyl citrate automated PA to include high-potency opioids with specific labeling that restricts their use to opioid-tolerant patients.

The specific automated PA criteria that will apply to the proposed drugs, as well as all fentanyl prescriptions, is:

- Patient is likely to be opioid-tolerant based on receiving at least one prescription for one of the following strong opioids (fentanyl transdermal, fentanyl transmucosal, morphine, oxycodone (not including combination products), hydromorphone, methadone, or oxymorphone) during the last 60 days.

After reviewing estimates of the number of utilizers affected by this expanded PA, the P&T Committee agreed to incorporate the high-potency opioids labeled for use in opioid-tolerant patients to the existing fentanyl citrate PA. The impact was estimated to be relatively small compared to the number of current fentanyl utilizers.

1. ***COMMITTEE ACTION: MODIFICATION OF FENTANYL PA AND IMPLEMENTATION***—To ensure the appropriate use of high-potency opioids in opioid-tolerant patients, the P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) modifying the fentanyl automated PA and including the following drugs:

    - morphine sulfate ER (MS Contin generics 100, 200 mg; Avinza 45, 60, 75, 90, 120 mg; Kadian 100, 200 mg);
    - morphine sulfate ER/naltrexone (Embeda 100/4mg);
    - fentanyl buccal soluble film (Onsolis 200, 400, 600, 800, 1200 mcg);
    - hydromorphone ER (Exalgo 8, 12, 16 mg); and
    - oxycodone ER (Oxycontin 60, 80, 160 mg)

The expanded fentanyl PA becomes effective the first Wednesday after a 60-day implementation period in all points of service. Based on the committee's recommendation, the effective date is April 13, 2011.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VII. ITEMS FOR INFORMATION

A. Effects of Formulary Changes—PORT: The PORT presented data on the effects of formulary changes in two drug classes: the LIP-1s, last reviewed in May 2010, and the Phosphodiesterase-5 Inhibitors (PDE-5s), last reviewed in November 2009. The P&T Committee requested further analysis as more data becomes available.

B. Simvastatin/Niacin ER (Simcor) Automated PA Update—Simvastatin/niacin ER (Simcor) is now available in 40/500 mg and 40/1000 mg tablets, with a maximum dose of 40 mg/2000 mg daily. P&T Committee was informed that the automated PA was updated to include the new simvastatin/niacin ER dosage strengths.

C. Clopidogrel-Proton Pump Inhibitor (PPI) Drug Interaction Update—The P&T Committee was briefed on the most recent information regarding a drug interaction between clopidogrel (Plavix) and PPIs. A previous update was provided to the P&T Committee in May 2009. Joint guidelines from the American College of Cardiology/American Heart Association/American College of Gastroenterology, published in November 2010, address concomitant use of PPIs with clopidogrel and other anti-platelet drugs. The P&T Committee recommended maintaining the current PPI MN and automated PA criteria, continued monitoring of literature and the FDA for new updates, and revisiting the issue when significant new developments occur.

D. Process For New Drug Pharmacy Benefit Determination—A proposed algorithm to determine whether a newly-marketed FDA-approved drug falls under the pharmacy benefit was presented. The proposed algorithm will be reviewed by the TRICARE Office of General Counsel.

VIII. FUTURE CLASS OVERVIEWS

Overviews for three drug classes were presented to the P&T Committee. The LIP-2s drug class is comprised of the fenofibric acid derivatives (gemfibrozil and the fenofibrates), prescription omega-3 fatty acids, and bile acids sequestrants. The nasal corticosteroids were previously reviewed by the P&T Committee in November 2005 and November 2008; they will be re-reviewed at an upcoming meeting. Information regarding the atypical antipsychotics drug class was also presented. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost-effectiveness models. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

IX. ADJOURNMENT

The meeting adjourned at 1700 hours on November 16, 2010, and at 1600 hours on November 17, 2010. The next meeting will be in February 2011.

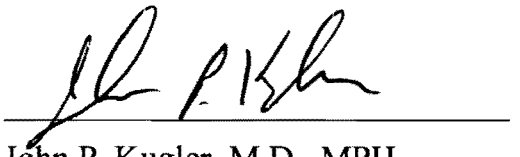
Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Appendix C—Table of Implementation Status of UF Recommendations/Decisions

Appendix D—Table of Abbreviations

SUBMITTED BY:



John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

, MD.

Jonathan Woodson, M.D.
Director

2/4/2011
(Date)

Appendix A—Attendance

Voting Members Present	
John Kugler, COL (Ret), MC, USA	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col George Jones, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Carole Labadie, MSC	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
LTC Jack Lewi, MC for COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Bart Staat, MC for Major Jeremy King, MC	Air Force, OB/GYN Physician
CAPT David Tanen, MC	Navy, Physician at Large
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LTC Mike Wynn, MC for LTC Bruce Lovins, MC	Army, Family Practice Physician
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Mr. Joe Canzolino	Department of Veterans Affairs
Dr. Miguel Montalvo	TRICARE® Regional Office-South Chief of Clinical Operations Division and Medical Director
Nonvoting Members Present	
Mr. David Hurt	Assistant General Counsel, TMA
LCDR Joe Lawrence, MSC	DoD PEC/TMA POD
CDR Michele Hupp, MSC	Defense Medical Standardization Board
Guests	
Brittany Martinez	Student, University of Incarnate Word Feik School of Pharmacy

Appendix A—Attendance (continued)

Guests	
Dr. Todd Semla	Veterans Affairs, Pharmacy Benefits Management Services
LCDR Kailee Fretland	United States Public Health Service/Indian Health Service
Others Present	
COL Cynthia Clagett, MC	DoD Pharmacoeconomic Center
Lt Col Rey Morales, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
LCDR Ola Ojo, MSC	DoD Pharmacoeconomic Center
HM1 Trishonya Mcmihelk	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Joshua Devine	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Medical Necessity Criteria for Newly-Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Metformin ER (Fortamet) Metformin ER (Glumetza) **Non-insulin Diabetes Drugs: Biguanides**	• Use of formulary agents contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives
Rosiglitazone (Avandia) Rosiglitazone/metformin (Avandamet) Rosiglitazone/glimepiride (Avandaryl) **Non-insulin Diabetes Drugs: Thiazolidinediones (TZDs)**	• Use of formulary agents contraindicated • The patient previously responded to a nonformulary agent, and changing to a formulary agent would incur unacceptable risk
Pitavastatin (Livalo) **Antilipidemics-1s**	• Use of formulary agents contraindicated
Fenofibrate (Fibricor) **Antilipidemics-2s**	• Use of formulary agents contraindicated
Estradiol valerate / dienogest (Natazia) **Contraceptive Agents**	• Use of formulary agents contraindicated • No alternative formulary agent available (if other oral contraceptive agents do not provide adequate bleeding and cycle control)

Appendix C—Table of Implementation Status of UF Recommendations/Decisions Summary Table

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2010	**Non-Insulin Diabetes Drugs** Biguanides	UF Review	▪ Metformin IR 500, 850, 1000 mg (generics) ▪ Metformin ER 500, 750 mg (generics)	▪ Metformin 500 mg/5mL liquid (Riomet)	▪ Metformin ER 500, 1000 mg (Fortamet) ▪ Metformin ER 500, 1000 mg (Glumetza) (Nov 2010)	Pending 60 days	Not applicable	Trial of metformin and/or sulfonylurea is mandated before TZDs, DPP-4 inhibitors or GLP-1 agonists can be used
Nov 2010	**Non-Insulin Diabetes Drugs** Sulfonylureas	UF Review	▪ Glipizide (generics) ▪ Glyburide (generics) ▪ Glyburide micronized tabs (generics)	▪ Chlorpropamide (generics) ▪ Glimepiride (generics) ▪ Glipizide ER (generics) ▪ Glipizide/metformin (generics) ▪ Glyburide/metformin (generics)	Not applicable (no drug designated nonformulary)	Pending 60 days	Not applicable	Trial of metformin and/or sulfonylurea is mandated before TZDs, DPP-4 inhibitors or GLP-1 agonists can be used
Nov 2010	**Non-Insulin Diabetes Drugs** Alpha Glucosidase Inhibitors	UF Review	Not applicable (no drug designated BCF)	▪ Acarbose (generics) ▪ Miglitol	Not applicable (no drug designated nonformulary)	Not applicable	Not applicable	-
Nov 2010	**Non-Insulin Diabetes Drugs** Meglitinides	UF Review	Not applicable (no drug designated BCF)	▪ Nateglinide (generics) ▪ Repaglinide (Prandin) ▪ Repaglinide/metformin (Prandimet)	Not applicable (no drug designated nonformulary)	Not applicable	Not applicable	-
Nov 2010	**Non-Insulin Diabetes Drugs** Thiazolidinediones	UF Review	Not applicable (no drug designated BCF)	▪ Pioglitazone (Actos) ▪ Pioglitazone/metformin (Actoplus Met) ▪ Pioglitazone/metformin XL (Actoplus Met XR) ▪ Pioglitazone/glimepiride (Duetact)	▪ Rosiglitazone (Avandia) ▪ Rosiglitazone/ metformin (Avandamet) ▪ Rosiglitazone/ glimepiride (Avandaryl) (Nov 2010)	Pending 60 days	Step Therapy (Automated PA)	Step Therapy (automated PA) with metformin and sulfonylureas as step preferred agents

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2010	**Non-Insulin Diabetes Drugs** DPP-4 Inhibitors	UF Review	▪ Sitagliptin (Januvia) ▪ Sitagliptin/Metformin (Janumet)	▪ Saxagliptin (Onglyza)	Not applicable (no drug designated nonformulary)	Pending 60 days	Not applicable	Step Therapy (automated PA) with metformin and sulfonylureas as step preferred drugs
Nov 2010	**Non-Insulin Diabetes Drugs** GLP-1 Receptor Agonists	UF Review	Not applicable (no drug designated BCF)	▪ Exenatide (Byetta) ▪ Liraglutide (Victoza)	Not applicable (no drug designated nonformulary)	Pending 60 days	Step Therapy (Automated PA) Manual PA precluding use of GLP-1s for obesity	-Step Therapy (automated PA) with metformin and sulfonylureas as step preferred drugs -Exenatide (Byetta) is step preferred for the GLP-1 subclass
Nov 2010	**Non-Insulin Diabetes Drugs** Amylin Agonist	UF Review	Not applicable (no drug designated BCF)	▪ Pramlintide (Symlin)	Not applicable (no drug designated nonformulary)	Pending 60 days	Manual PA expanded to preclude the use of Symlin for obesity	
Nov 2010	Newer Insomnia	New Drug Doxepin (Silenor)	▪ Zolpidem IR	▪ **Doxepin (Silenor) (Nov 2010)** ▪ Eszopiclone (Lunesta)	▪ Zolpidem CR (Ambien CR) ▪ Zaleplon (Sonata) ▪ Ramelteon (Rozerem) ▪ Zolpidem sublingual (Edluar)	Not applicable	Step Therapy (Automated PA)	Doxepin (Silenor) remains UF Step Therapy applies with zolpidem IR preferred
Nov 2010	Pulmonary-1 ICS/LABA	New Drug Formoterol/ mometasone (Dulera)	▪ Fluticasone/salmeterol (Advair Diskus and HFA)	▪ **Formoterol/ mometasone (Dulera) (Nov 2010)** ▪ Budesonide/formoterol (Symbicort)	Not applicable (no drug designated nonformulary)	Not applicable	QLs apply Retail: 1 MDI/30 d Mail order: 3 MDIs/90 d	

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Nov 2010	Antilipidemic Agents I	• *New Drug* Pitavastatin (Livalo)	▪ Atorvastatin (Lipitor) ▪ Pravastatin (Pravachol, generics) ▪ Simvastatin (Zocor, generics)	▪ Atorvastatin / amlodipine (Caduet) ▪ Ezetimibe (Zetia) ▪ Ezetimibe / simvastatin (Vytorin) ▪ Fluvastatin IR/ER (Lescol) ▪ Lovastatin IR ▪ Lovastatin ER (Altoprev) ▪ Lovastatin / niacin ER (Advicor) ▪ Niacin ER (Niaspan) ▪ Rosuvastatin (Crestor) ▪ Simvastatin/ niacin ER (Simcor)	▪ **Pitavastatin (Livalo) (Nov 2010)**	Pending 60 days	Step Therapy (Automated PA)	▪ Pitavastatin (Livalo) designated non-formulary ▪ Step therapy (automated PA) with generics or atorvastatin as the preferred drugs (note: step therapy doe apply to ezetimibe or ni
Nov 2010	Antilipidemic Agents II	• *New Drug* Fenofibric acid (Fibricor) ▪ *BCF removal* Fenofibrate meltdose (Fenoglide)	▪ Gemfibrozil (Lopid)	▪ Fenofibrate meltdose (Fenoglide) ▪ Fenofibrate IDD-P (micronized) (Triglide) ▪ Fenofibrate micronized/nonmicronized (Lofibra) ▪ Cholestyramine / aspartame (Questran Light, Prevalite Locholest Light) ▪ Cholestyramine / sucrose (Questran) ▪ Colestipol (Colestid)	▪ **Fenofibric acid (Fibricor) (Nov 2010)** ▪ Fenofibrate nanocrystallized (Tricor) ▪ Fenofibrate micronized (Antara) ▪ Fenofibric acid (Trilipix) ▪ Omega-3 fatty acids (Lovaza) ▪ Colesevelam (Welchol)	Pending 60 days	Not applicable	▪ Fenofibric acid (Fibricor) recommended for NF (pending) ▪ Fenofibrate meltdose (Fenoglide) removed from BCF and recommended for UF(pending)
Nov 2010	Contraceptive Agents	• *New Drug* Estradiol valerate/ dienogest (Natazia)	▪ See TRICARE formulary search tool*	▪ See TRICARE formulary search tool*	▪ **Estradiol valerate/dienogest (Natazia) (Nov 2010)** ▪ See TRICARE formulary search tool* for remainder of NF drugs	Pending 60 days	Not applicable	▪ Estradiol valerate/dienogest (Natazia) recommended for NF (pending) ▪ Contraceptives update in 2011

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Feb 2010	Narcotic Analgesics	• *New Drug* Hydromorphone ER (Exalgo)	▪ morphine sulfate IR 15, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	▪ **Hydromorphone ER (Exalgo) (Nov 2010)** ▪ Fentanyl buccal soluble film (Onsolis) ▪ Fentanyl transdermal system, transmucosal tablet (Fentora); & transmucosal lozenge ▪ Codeine ▪ Hydromorphone (Dilaudid) ▪ Levorphanol ▪ Meperidine ▪ Methadone ▪ Morphine products (other than BCF), Kadian and Avinza (ER products) ▪ Morphine sulfate ER / naltrexone (Embeda) ▪ Opium tincture ▪ Opium/belladonna alkaloids(suppositories) ▪ Oxycodone IR ▪ Oxycodone ER(Oxycontin) ▪ Oxymorphone (Opana) ▪ Oxycodone/ASA ▪ Oxycodone/APAP not BCF ▪ Buprenorphine injection ▪ Butorphanol ▪ Pentazocine/naloxone ▪ Propoxyphene ▪ Nalbuphine ▪ Codeine / APAP(not BCF) ▪ Codeine/ASA+ carisoprodol ▪ Codeine/caffeine butalbital/APAP or ASA ▪ Dihydrocodeine / caffeine / APAP or ASA ▪ Hydrocodone / APAP ▪ Pentazocine / APAP ▪ propoxyphene / APAP ▪ Propoxyphene/ASA/caffeine ▪ Tramadol / APAP	▪ Tramadol ER (Ultram ER) Feb 07 ▪ Tramadol ER (Ryzolt) Nov 09 ▪ Tapendatol (Nucynta) Nov 09	Not applicable	Not applicable	Hydromorphone ER remains UF (pending)

ASA: aspirin
APA: acetaminophen
DPP-4: dipeptidyl peptidase-4
ER: extended release
ECF: Extended Core Formulary
GLP-1: glucagon-like peptide 1
ICS/LABA: inhaled corticosteroid/long-acting beta agonist
IDD-P: insoluble drug deliver particle
IR: immediate release
MDI: metered dose inhaler
*TRICARE Formulary Search tool: http://www.pec.ha.osd.mil/formulary_search.php

Appendix D—Table of Abbreviations

ADA	American Diabetes Association
AGIs	alpha-glucosidase inhibitors
Avg CER	average cost effectiveness ratio
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CMA	cost minimization analysis
CV	Cardiovascular
DM	diabetes mellitus
DPI	dry powder inhaler
DPP-4	dipeptidyl-peptidase 4 inhibitor subclass
DoD	Department of Defense
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
FSS	Federal Supply Schedule Price
FPG	fasting plasma glucose
GI	gastrointestinal
GLP1RA	glucagon-like peptide-1 receptor agonist subclass
HA	Health Affairs
HDL	high density lipoprotein cholesterol
HbA1c	glycosolated hemoglobin or hemoglobin A1c
ICS/LABA	inhaled corticosteroid / long-acting beta agonist
IR	immediate release
LDL	low density lipoprotein cholesterol
LIP-1	Antilipidemic-1s drug class
MARR	Mandatory Agreement for Retail Refunds
MHS	Military Health System
MI	myocardial infarction
MDI	metered dose inhaler
MEN2	Endocrine Neoplasia syndrome type 2
MS	multiple sclerosis
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
OMB	Office of Management and Budget
OROS	osmotic controlled release oral delivery system
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
P1	Period 1
PPG	post prandial glucose

Appendix D—Table of Abbreviations (continued)

PPI	proton pump inhibitor drug class
PORT	Pharmaceutical Outcomes Research Team
QL	quantity limit
Rxs	prescriptions
SED-1	sedative hypnotic-1 drug class
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCA	tricyclic antidepressant
TG	triglyceride
SR	sustained release
TZD	thiazolidinedione subclass
UKPDS	United Kingdom Prospective Diabetes Study
VA	Veteran's Affairs

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
August 2010

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 11, and 12, 2010, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of May minutes**—Dr. Charles Rice, Acting Director, approved the minutes for the May 2010 DoD P&T Committee meeting on July 23, 2010.
2. **Clarification of May minutes**—The Basic Core Formulary (BCF) recommendation for the alpha blocker terazosin was clarified to specify generic formulations—not proprietary formulations—are included on the BCF.
3. **Clarifications of February 2010 Minutes**—The clinical effectiveness conclusion for the antihemophilic agents regarding purified factor VIII and IX concentrates was clarified to state:

> "National professional group guidelines, including the National Hemophilia Foundation Medical and Scientific Advisory Committee (MASAC 159) and national hemophilia patient advocacy groups caution against switching between products once a patient is stabilized."

III. UNIFORM FORMULARY (UF) DRUG CLASS REVIEWS

A. Renin Angiotensin Antihypertensive Agents (RAAs)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the RAAs drug class. The class is comprised of the Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), the Direct Renin Inhibitors (DRIs), and their fixed-dose combination (FDC) products with hydrochlorothiazide (HCTZ), calcium channel blockers (CCBs), or other RAAs. The ARBs were previously reviewed by the P&T Committee in May 2007 and February 2005; ACE Inhibitors were previously reviewed in August 2005; and the fixed-dose combination ACE Inhibitor/CCB products were previously reviewed in February 2006.

The clinical review included, but was not limited to, sources of information listed in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

The individual RAAs are listed below:

- **ACE Inhibitors:** benazepril (Lotensin, generic), benazepril/HCTZ (Lotensin HCT, generic), captopril (Capoten, generic), captopril/HCTZ (Capozide, generic), enalapril (Vasotec, generic), enalapril/HCTZ (Vasoretic, generic), fosinopril (Monopril, generic), fosinopril/HCTZ (Monopril HCT, generic), lisinopril (Prinvil, Zestril, generic), lisinopril HCT (Prinzide, Zestoretic, generic), moexipril (Univasc, generic), moexipril/HCTZ (Uniretic generic), perindopril (Aceon, generic), quinapril (Accupril, generic) quinapril/HCTZ (Accuretic, generic), trandolapril (Mavik, generic), and ramipril (Altace, generic)
- **ARBs:** candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan, (Teveten), eprosartan/ HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), losartan (Cozaar, generic), losartan/HCTZ (Hyzaar, generic), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), telmisartan (Micardis), telmisartan/ HCTZ (Micardis HCT), valsartan (Diovan), and valsartan/HCTZ (Diovan HCT)
- **DRIs:** aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), and valsartan/aliskiren (Valturna)
- **Fixed dose combinations:** (RAAs/CCBs): benazepril/amlodipine (Lotrel, generic), trandolapril/verapamil sustained release (SR) (Tarka, generic), olmesartan/amlodipine (Azor), telmisartan/amlodipine (Twynsta), valsartan/amlodipine (Exforge), and valsartan/amlodipine/HCTZ (Exforge HCT)

The current BCF products are lisinopril, lisinopril/HCTZ, ramipril, and benazepril/amlodipine. The nonformulary (NF) agents include perindopril, moexipril +/- HCTZ, trandolapril/verapamil sustained release (SR), eprosartan +/- HCTZ, irbesartan +/-HCTZ, olmesartan +/- HCTZ, valsartan +/-HCTZ, olmesartan/amlodipine, telmisartan/amlodipine, valsartan/amlodipine, and aliskiren/valsartan. The remaining drugs are classified as UF drugs. Generic formulations are available for all the ACE inhibitors and the ACE inhibitor/diuretic products; generic formulations of losartan and losartan/HCTZ entered the market in April 2010. Generic formulations of candesartan, irbesartan, and valsartan are expected in 2012.

The RAAs class is ranked within the top 5 most costly Military Health System (MHS) drug classes, with expenditures exceeding $300 million annually. In terms of utilization, the ACE inhibitors comprise 58% of the RAAs market share, with the ARBs comprising 36%, and the fixed-dose combinations comprising 6%. For expenditures, the ARBs account for 66% of the annual MHS cost for the RAAs.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the RAAs:

1. For treating hypertension, the results of one systematic review reported the ARBs reduce blood pressure (BP) to a similar degree; at maximum recommended doses, the average trough systolic blood pressure reduction is -8 mmHg and the average trough diastolic blood pressure reduction is -5 mmHg.
2. The ACE inhibitors, ARBs, and the DRI aliskiren (Tekturna) reduce BP to a similar degree, based on the conclusions from two systematic reviews.
3. The addition of HCTZ increases the BP-lowering efficacy of the RAAs. The current Joint National Committee (JNC) 7 hypertension guidelines recommend multidrug regimens include a thiazide diuretic (e.g., HCTZ).
4. Hypertension studies show that the FDC products produce significantly greater BP reductions than their individual components. Additional benefits of FDC products include potential enhanced medication compliance, and simplified medication regimens. Disadvantages include loss of flexibility for dosage initiation and titration.
5. All the ARBs are U.S. Food and Drug Administration (FDA)-approved for treating hypertension; some of the ARBS have shown evidence for positive clinical outcomes. Telmisartan (Micardis) is FDA-approved to reduce the risk of cardiovascular (CV) mortality and morbidity in patients who are at high risk for CV events and are intolerant of ACE inhibitors (ON-TARGET and TRANSCEND trials). Candesartan (Atacand) and valsartan (Diovan) are FDA-approved for reducing the risk of death and hospitalization in patients with chronic heart failure. Losartan (Cozaar, generic) and irbesartan (Avapro) are FDA-approved to reduce the risk of delaying progression to end-stage renal disease (ESRD), doubling of serum creatinine, or death in patients with Type 2 diabetes mellitus (DM).
6. Although losartan (Cozaar, generic) is currently not FDA-approved for treating chronic heart failure, data from one trial (HEAAL, Lancet

2010) reported losartan 150 mg reduced the risk of death or hospitalization due to heart failure.

7. One unpublished trial (ORIENT) with olmesartan in patients with Type 2 DM did not find a delayed progression to ESRD, doubling of serum creatinine, or death. Another unpublished trial (ROADMAP) evaluating olmesartan in Type 2 DM patients did find a benefit in the surrogate outcome of delaying progression to microabluminuria.
8. For the RAA/CCB products, benazepril/amlodipine (Lotrel, generic) was superior to benazepril/HCTZ (Lotensin HCT, generic) in reducing the composite of CV mortality and morbidity in patients with hypertension who are at high risk for CV events (ACCOMPLISH trial). Benazepril/amlodipine is the only RAA/CCB FDC product with evidence for positive clinical outcomes, in addition to reducing BP.
9. There is no data to suggest that there are clinically relevant differences in the BP-reducing efficacy of the ARB/CCB FDC products olmesartan/amlodipine (Azor), telmisartan/amlodipine (Twynsta), or valsartan/amlodipine (Exforge). Adding an ARB to amlodipine results in a lower incidence of peripheral edema than that reported with CCB monotherapy.
10. Valsartan/amlodipine/HCTZ (Exforge HCT) is the first triple FDC antihypertensive drug to obtain FDA approval. It is more effective at reducing BP than administering two antihypertensive drugs, but has a higher incidence of orthostatic hypotension and dizziness than two-drug regimens.
11. The DRI aliskiren (Tekturna) reduces BP by suppressing plasma renin activity, which is unique among the RAAs. Aliskiren is effective at reducing BP when used as monotherapy or in combination with other antihypertensive drugs, but the BP effects are similar to that achieved with the diuretics, ARBs, or ACE inhibitors. Aliskiren is approved solely for treating hypertension; clinical outcomes trials are ongoing. Current JNC guidelines do not address the place in therapy for the DRIs. The adverse event profile for aliskiren appears similar to the ARBs.
12. Adding HCTZ to aliskiren (Tekturna HCT) provides enhanced BP reduction and is consistent with JNC guidelines, due to the diuretic component. There is limited published information for aliskiren/ HCTZ.

13. Aliskiren/valsartan (Valturna) is the first DRI/ARB that is FDA-approved for hypertension; it provides another option for patients requiring multidrug antihypertensive regimens. However, there are only limited published studies available, it is approved solely for treating hypertension, and the benefits of dual RAA inhibition are debatable, due to an increased risk of adverse events.
14. For the ACE inhibitors, with the exception of moexipril (Univasc, generics), evidence exists for positive clinical outcomes (e.g., decreased risk of major CV events or death in high-CV risk patients, those with heart failure, in patients with Type 2 diabetic renal disease, or in the post-myocardial (MI) setting), in addition to lowering BP.
15. For the ARBs, it is unlikely that there are clinically relevant differences in their adverse event profiles. Clinical trials show similar adverse event rates as with placebo.
16. The FDA is evaluating the association of ARBs and an increased risk of cancer, which was reported in a recent meta-analysis (Sipahi, et al., Lancet Oncology 2010). The FDA maintains the benefits of ARBs currently outweigh their risk.
17. The FDA is evaluating the risk of increased CV death with olmesartan reported in Type 2 DM patients from the ROADMAP and ORIENT trials. FDA is currently reviewing the data for olmesartan and has not concluded that it increases the risk of death.
18. For the ACE inhibitors, the major adverse events are hyperkalemia, increased serum creatinine, and cough. One systematic review comparing the ARBs with the ACE inhibitors reported the overall incidence of ACE inhibitor-induced cough as ranging between 0%–23% (mean 10%).
19. The DoD Pharmacy Outcomes Research Team (PORT) provided an analysis of RAAs MHS prescription data and reported that ARBs are initiated as first-line therapy in the majority of patients, instead of ACE inhibitors. Additionally, it does not appear that patients with comorbidities (chronic heart failure, DM, left ventricular hypertrophy, post-MI) are prescribed an ARB based on the evidence for positive outcomes data and hypertension.
20. A survey of Military Treatment Facility (MTF) providers regarding the place in therapy using RAAs for hypertension revealed the ACE inhibitors are considered first-line, the ARBs are second-line, and the DRIs are third-line. The majority of providers responded that ARBs are interchangeable for

treating hypertension. Most respondents did not agree that FDC products were necessary to treat the majority of their hypertensive patients.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the RAAs. Cost-minimization analyses (CMAs) and budget impact analyses (BIAs) were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the RAAs subclasses of ACE inhibitors, ARBs, DRIs, and FDC products with HCTZ, CCBs, or other RAAs were similar with regard to treating hypertension. For the cost effectiveness analysis, the FDC products were compared with their parent RAA. Products containing aliskiren were analyzed and incorporated into the CMA and BIA used to evaluate the ARB subclass.

Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

- **ACE Inhibitors and their combinations with HCTZ and/or CCBs:** Because all ACE inhibitors are now available in generic formulations, comparisons were made against the ARBs, ARB/combinations, DRIs, and DRI/combinations in the form of an ACE inhibitor step-therapy model. BIA was used to assess the potential impact of cost scenarios where ACE inhibitors or their combination agents were designated as the step-preferred agents on the UF prior to filling a prescription for ARBs, DRIs, or their respective combination products. Cost scenarios evaluating the impact of designating ACE inhibitors or ACE inhibitors/combinations as BCF agents prior to the use of ARBs, DRIs, or their respective combinations were also considered. BIA results showed that requiring an ACE inhibitor prior to using any ARB, DRI, or their respective combinations would be cost effective. Due to existing prescribing practices in the MHS, the P&T Committee agreed that use of an ACE inhibitor as a required step-preferred therapy could not be operationalized in an Automated Prior Authorization (PA).
- **ARBs, ARB/combinations, DRIs, and DRI/combinations:** BIA was used to assess the potential impact of cost scenarios where selected ARBs, ARB/combinations, DRIs, and DRI/combinations were designated as formulary or NF on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered. BIA results for the ARBs and DRIs showed the scenario placing losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/ HCTZ (Micardis HCT), telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), and valsartan/amlodipine/HCTZ (Exforge HCT) as step-preferred agents, while

placing all other ARBs, ARB/combinations, DRIs, and DRI/combinations on the UF was the most cost-effective scenario and operationally-appropriate choice.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the RAAs.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

    a) losartan, losartan/HCTZ, telmisartan (Micardis), and telmisartan/HCTZ (Micardis HCT), remain classified as formulary on the UF, and that telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge) and valsartan/amlodipine/HCTZ (Exforge HCT) be designated formulary on the UF. Prior authorization (PA) for the RAAs drug class would require a trial of one of these step-preferred drugs for new patients (15 for, 0 opposed, 1 abstained, 0 absent);

    b) aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), olmesartan/amlodipine (Azor), and valsartan/aliskiren (Valturna), be designated formulary on the UF (non-preferred) (15 for, 0 opposed, 1 abstained, 0 absent);

    c) benazepril, benazepril HCTZ, benazepril/amlodipine, captopril, captopril HCTZ, enalapril, enalapril HCTZ, fosinopril, fosinopril HCTZ, lisinopril, lisinopril HCTZ, quinapril, quinapril HCTZ, ramipril, and trandolapril remain formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

    d) The following four ACEs previously designated NF on the UF are now available in cost-effective generic formulations and will be designated formulary on the UF: moexipril (Univasc), moexipril HCTZ (Uniretic), perindopril (Aceon), and trandolapril/verapamil (Tarka) (15 for, 0 opposed, 1 abstained, 0 absent).

e) As a result of the above recommendations, there are no RAAs designated as nonformulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved 11/10/10

Approved, but modified as follows:

2. ***COMMITTEE ACTION: PA CRITERIA***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria should apply to the non-preferred RAAs, aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), aliskiren/valsartan (Valturna), candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), and olmesartan/amlodipine (Azor). Coverage would be approved if the patient met any of the following criteria:

   a) Automated PA criteria:

      (1) The patient has received a prescription for losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

   b) Manual (paper) PA criteria, if automated criteria are not met:

      (1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

      (2) The patient has tried one of the preferred RAAs and has had an inadequate response.

      (3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

Acting Director, TMA, Decision: ☒*Approved* □ *Disapproved*

11/10/10

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 2 absent) an effective date an effective date of first Wednesday after a 60 days implementation period in all points of service. The effective date is 12 Jan 2011.

Acting Director, TMA, Decision: ☒ Approved □ Disapproved

11/8/10

Approved, but modified as follows

4. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended:
    a) losartan, losartan HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT), valsartan (Diovan), valsartan/HCTZ (Diovan HCT) be designated with BCF status (15 for, 0 opposed, 1 abstained, 0 absent);
    b) captopril, benazepril/amlodipine (Lotrel generics), lisinopril, lisinopril HCTZ, ramipril remain on the BCF (15 for, 0 opposed, 1 abstained, 0 absent).

Acting Director, TMA, Decision: ☒Approved □ Disapproved

11/8/10

Approved, but modified as follows:

B. Ophthalmic-1s

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the agents in the Ophthalmic-1 drug class. The class is comprised of the ophthalmic antihistamines (AHs), mast cell stabilizers (MCS), dual action AH/MCS, and the nonsteroidal anti-inflammatory drugs (NSAIDs). The Ophthalmic-1s have not previously been reviewed for UF placement; all the drugs are currently designated with formulary status on the UF, and there are no BCF or NF drugs. The clinical review focused on use of the Ophthalmic-1s for allergic conjunctivitis (AC) and included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The individual Ophthalmic-1s are listed below:

- **Antihistamines:** emedastine (Emadine)
- **Dual Action Antihistamine/Mast Cell Stabilizers:** azelastine (Optivar, generics), bepotastine (Bepreve), epinastine (Elestat), olopatadine 0.1% (Patanol), and olopatadine 0.2% (Pataday)
- **Mast Cell Stabilizers:** pemirolast (Alamast), nedocromil (Alocril), cromolyn (Crolom/Opticrom, generic), and lodoxamide (Alomide)
- **NSAIDs:** ketorolac 0.4% (Acular LS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), bromfenac (Xibrom), diclofenac (Voltaren, generic), flurbiprofen (Ocufen, generics), and nepafenac (Nevanac)

MHS expenditures for the Ophthalmic-1s exceed $19 million annually. In the MHS, olopatadine 0.2% (Patanol) is the highest utilized Ophthalmic-1 agent.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the Ophthalmic-1s:

1. With regard to mechanism of action and pharmacokinetic properties, the antihistamines provide relief of ocular itching, hyperemia, and edema, while MCS have anti-inflammatory effects. The dual action AH/MCS exhibit both properties. MCS have a slower onset of action for providing relief of ocular symptoms than AH/MCS (days to weeks, vs. minutes, respectively). NSAIDs relieve pain and reduce erythema.
2. With regard to FDA-approved indications, dual action AH/MCS and the MCS are approved for treating AC. For the NSAIDs, ketorolac 0.5% (Acular, generic) is approved for AC, and clinical trial data supports use of bromfenac (Xibrom) for this indication.

3. With regard to place in therapy, professional guidelines from the American Academy of Ophthalmology and the American Optometric Association recommend use of AHs or AH/MCS as first-line topical therapy for relief of AC symptoms.
4. With regard to efficacy for the treatment of AC, the results of one meta-analysis reported the following: MCS and AHs are superior to placebo in relieving symptoms of AC; there is no significant difference between the AHs and MCS in terms of proportion of patients with perceived benefit; there is insufficient evidence to demonstrate superiority of agents within each subclass; and convenience of use, cost and patient preference should guide treatment choice.
5. Interpretation of clinical efficacy differences between the individual dual action AH/MCS and individual MCS is difficult due to small patient enrollment, short-term treatment, use of single-dose studies, and acute course of symptoms. There are no head-to-head trials comparing bepotastine (Bepreve) with another Ophthalmic-1 agent. Overall, for relief of ocular itching, there does not appear to be clinically relevant differences between the dual action AH/MCS and the MCS.
6. With regard to safety and tolerability, published data does not suggest there are clinically relevant differences concerning burning/stinging, headaches, taste perversion, and hyperemia between the individual dual action AH/MCS and individual MCS in treating AC. The only published available meta-analysis did not assess adverse events, and the head-to-head trials were too small to determine clinically relevant differences individual dual action AH/MCS and individual MCS. The overall adverse event rate is low.
7. Data from the product labeling reports the dual action AH/MCS bepotastine (Bepreve) is associated with taste perversion in 25% of patients. For the MCS, nedocromil (Alocril) has an incidence of burning/stinging on instillation, plus taste perversion in 10%–30% of patients. The 0.5% concentration of ketorolac (Acular) is associated with burning/stinging in up to 40% of patients.
8. With regard to dosing frequency, olopatadine 0.2% (Pataday) is the only dual action AH/MCS that is dosed once daily; the other AH/MCS are dosed twice daily. For the MCS, nedocromil (Alocril) is dosed twice daily, while the other MCS are dosed 4–6 times daily. The NSAID ketorolac 0.5% (Acular) is dosed four times daily for AC.
9. With regard to preservatives, it remains to be determined whether the presence of carboxymethylcellulose instead of benzalkonium chloride

(BAK) in ketorolac 0.45% (Acuvail) or the reduced BAK concentration in bepotastine (Bepreve) are associated with a lower risk of adverse events.

10. A request for input from MTF providers revealed that the majority of responders ranked olopatadine 0.2% (Patanol) as the preferred Ophthalmic-1 agent to treat AC and olopatadine 0.1% (Pataday) as the second preference. The majority of responders chose cromolyn (Crolom/Opticrom, generic) as the preferred MCS, and ketorolac 0.5% (Acular, generic) as the preferred NSAID for treating AC.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the agents in the Ophthalmic-1 drug class used in the treatment of AC. CMAs and BIAs were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the Ophthalmic-1 subclasses were similar. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

- **Antihistamines and Dual Action AH/MCS:** Emedastine (Emadine) was analyzed with the dual action AH/MCS subclass. CMA results showed olopatadine 0.1% (Patanol) to be the most cost-effective agent for the treatment of AC, based on the cost per day of treatment. BIA was used to assess the potential impact of cost scenarios where Emedastine (Emadine) and/or dual action AH/MCS were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results from this analysis showed the most cost-effective scenario designated bepotastine (Bepreve) and epinastine (Elestat) NF on the UF, and the remaining dual action AH/MCS as formulary on the UF. Follow-up P&T Committee discussion considered the potential for MTF recapture of bepotastine (Bepreve) and epinastine (Elestat) from the retail sector to recommend formulary status for all other antihistamines and dual action AH/MCS agents.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) to accept the relative cost-effectiveness analysis of the Antihistamines and Dual Action AH/MCS subclass.

- **Mast Cell Stabilizers:** BIA was used to assess the potential impact of cost scenarios where selected MCS were designated formulary or NF on the UF.

Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed the most cost-effective scenario designated cromolyn 0.4% (generic) with formulary status on the UF, with all other MCS designated as NF on the UF. However, P&T Committee discussion recommended that all MCS should remain formulary on the UF because they are primarily prescribed by specialists and have low MHS low utilization.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the Mast Cell Stabilizers subclass.

- **Ophthalmic-1 NSAIDs:** BIA was used to assess the potential impact of cost scenarios where selected Ophthalmic-1 NSAIDs were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents with BCF status were also considered. This subclass is more commonly used in the treatment of post-surgical procedures than in the treatment of AC. BIA results showed that the most cost-effective scenario designated ketorolac 0.5% (generic Acular) with BCF status, with all other Ophthalmic-1 NSAIDs designated formulary on the UF. After discussion, the P&T Committee recommended against designating a BCF Opthmalic-1 NSAID because the majority of use is by ophthalmologic specialists for post-surgical procedures rather than primary care providers for AC.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the Ophthalmic-1 NSAIDs subclass.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:
    a) **Antihistamines and Dual Action AH/MCS:** azelastine (Optivar, generics), bepotastine (Bepreve), emedastine (Emadine), epinastine (Elestat), olopatadine 0.1% (Patanol), and olopatadine 0.2% (Pataday) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

b) **Mast Cell Stabilizers:** cromolyn (generic), lodoxamide (Alomide), nedocromil (Alocril), and pemirolast (Alamast) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

c) **NSAIDs:** bromfenac 0.09% (Xibrom), diclofenac 0.1% (Voltaren, generic), flurbiprofen 0.03% (Ocufen, generic), ketorolac 0.4% (Acular LS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), and nepafenac 0.1% (Nevanac) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved 11/10/10

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended upon signing of the minutes:

   a) **Antihistamines and Dual Action AH/MCS:** olopatadine 0.1% (Patanol) be added to the BCF (15 for, 0 opposed, 1 abstained, 0 absent).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved 11/10/10

Approved, but modified as follows:

IV. UTILIZATION MANAGEMENT—QUANTITY LIMITS (QL)

A. Tramadol ODT (Rybix)—QL: A new orally disintegrating formulation (ODT) of tramadol (Rybix) has been marketed. Tramadol ODT will be reviewed for UF status at an upcoming P&T Committee meeting as a newly-approved drug in the narcotic analgesic drug class. QLs are currently in place for both immediate and extended-release tramadol (Ultram, Ultram ER, generics).

1. ***COMMITTEE ACTION: QL***—The P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) to recommend QLs for tramadol ODT of 720 tablets/90 days in the mail order pharmacy and 240 tablets/30 days in the retail network, which is consistent with the recommended dosing from the product labeling and safety concerns.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

11/10/10

Approved, but modified as follows:

B. Ondansetron soluble film (Zuplenz)—QL: An oral soluble film of ondansetron (Zuplenz) is now on the market. Zuplenz will be reviewed as a new FDA-approved drug in the anti-emetic drug class at an upcoming P&T Committee meeting. QLs are currently in place for other formulations of ondansetron and the remainder of the 5-HT3 receptor antagonists in the class.

1. ***COMMITTEE ACTION: QL***— The P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) to recommend QLs for ondansetron soluble film of 180 tablets/90 days in the mail order pharmacy and 60 tablets/30 days in the retail network, which is consistent with the recommended dosing from the product labeling and avoids breaking apart packages for dispensing.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

11/10/10

Approved, but modified as follows:

C. Certolizumab Pegol Injection (Cimzia Starter Kit)—QL: A new starter kit of certolizumab pegol pre-filled syringes (Cimzia) for Crohn's disease has been marketed. Cimzia was reviewed as a new FDA-approved drug in the targeted immunomodulatory biologics (TIB) drug class in August 2009. This starter kit provides for a loading dose required at initiation of therapy. QLs are currently in place for the other formulations of certolizumab pegol and the remainder of the TIBs products.

1. ***COMMITTEE ACTION: QL***—The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to recommend QLs for certolizumab pegol of 1 kit (6 syringes) with no refills in the mail order pharmacy and 1 kit (6 syringes) with no refills in the retail network, which is consistent with the recommended dosing from the product labeling and avoids breaking apart packages.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved 11/10/10

Approved, but modified as follows:

D. Nilotinib Capsules (Tasigna)—QL: Nilotinib (Tasigna) is a kinase inhibitor that is approved for treating Philadelphia chromosome-positive chronic myeloid leukemia. QLs are currently in place for imatinib (Gleevec) and oral antineoplastic agents, due to the potential for drug discontinuations or dosage changes due to adverse effects, drug interactions, or patient response to therapy.

1. ***COMMITTEE ACTION: QL***— The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to recommend QLs for nilotinib of 224 capsules/56 days in the mail order pharmacy and 112 capsules/28 days in the retail network, which is consistent with the recommended dosing from the product labeling and safety concerns.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved 11/10/10

Approved, but modified as follows:

V. ITEMS FOR INFORMATION

A. Pharmacy Outcomes Research Team—The PORT briefed the P&T Committee on the utilization and expenditures for several of the UF drug classes previously reviewed by the P&T Committee. Additional updates will be provided at upcoming meetings.

B. Thiazolidinedione (TZD) Safety Update—The P&T Committee reviewed updated safety information for rosiglitazone. Additional information will be provided when the TZD drug class review is presented at the November 2010 P&T Committee Meeting.

C. **PA for Quinine Sulfate Safety Update**—The P&T Committee reviewed new FDA-mandated safety requirements for quinine sulfate (Qualaquin). Prior Authorization for Qualaquin restricting use for malaria was recommended at the May 2010 P&T Committee Meeting. In July 2010, an FDA safety communication stated Qualaquin should only be used for malaria, warned of safety issues when used off-label for leg cramps; and required the manufacturer to develop a risk evaluation and mitigation strategy program.

D. **BCF Consensus Statement** —The P&T Committee stated its position that BCF-designated drugs will be stocked in the Pharmacy or readily available on the next duty day for MTFs located in the continental United States (CONUS), and be readily available on the next available order for MTFs located outside the continental United States (OCONUS).

VI. CLASS OVERVIEWS

Overviews for two drug classes were presented to the P&T Committee. The inflammatory bowel disease/irritable bowel syndrome drug class is comprised of the 5-aminosalicylates, gastrointestinal steroids, and the 5-HT3 antagonists. The pancreatic enzymes were also reviewed. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost-effectiveness models. The clinical and economic analyses of these classes will be presented at an upcoming meeting.

VII. ADJOURNMENT

The meeting adjourned at 1620 hours on August 11, 2010, and at 0945 hours on August 12, 2009. The next meeting will be in November 2010.

Appendix A—Attendance

Appendix B—Table of Implementation Status of UF Recommendations/Decisions

Appendix C—Table of Abbreviations

SUBMITTED BY:

Actual Signing date was 8 NOV 2010

John P. Kugler, MD, MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

George Peach Taylor, Jr., MD, MPH
Acting Director

11/18/2010
(Date)

Appendix A—Attendance

Voting Members Present	
Dr. John Kugler, COL (Ret), USA, MC	DoD P&T Committee Interim Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center (Recorder)
Col Everett McAllister, BSC	Deputy Chief, Pharmaceutical Operations Directorate
COL Carole Labadie, MS	Army, Pharmacy Officer
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
CAPT David Tanen, MC	Navy, Physician at Large
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LTC Bruce Lovins, MC	Army, Family Practice Physician
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
CDR Eileen Hoke, MC	Navy, Pediatrics
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Assistant General Counsel, TMA
CDR Michele Hupp, MSC	Defense Medical Standardization Board
Guests	
Col George Jones, BSC	Pharmaceutical Operations Directorate
Major Achilles Hamilothoris	Defense Logistics Agency Troop Support
Dr. David Trang	University of Incarnate Word Pharmacy School
Melinda Neuhauser	Veterans Affairs, Pharmacy Benefits Management Services
CDR Tamara Close	United States Public Health Service/Indian Health Service

Appendix A—Attendance (continued)

Others Present	
COL Cynthia Clagett	DoD Pharmacoeconomic Center
Lt Col Rey Morales	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
LCDR Ola Ojo	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacoeconomic Center
Dr. Amy Lugo	DoD Pharmacoeconomic Center
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B—Table of Implementation Status of UF Recommendations/Decisions

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2010	Renin Angiotensin Anti-Hypertensives (RAAs)	UF Review	**ACE Inhibitors** ▪ Lisinopril (Prinvil, Zestril, generic) ▪ lisinopril HCT (Prinzide, Zestoretic generic) ▪ Captopril (Capoten, generic) ▪ Ramipril (Altace, generic) **ACE-Inhibitor/CCB** ▪ Benazepril/amlodipine (Lotrel, generic) **ARBs** ▪ Losartan (Cozaar, generic) ▪ Losartan/HCTZ (Hyzaar, generic) ▪ Telmisartan (Micardis) ▪ Telmisartan/ HCTZ (Micardis HCT) ▪ Valsartan (Diovan) ▪ Valsartan/HCTZ (Diovan HCT)	**ACE Inhibitors** ▪ Benazepril +/- HCTZ (Lotensin, Lotensin HCT generic) ▪ Captopril/HCTZ (Capozide, generic) ▪ Enalapril, Enalapril/HCTZ (Vasotec, Vasoretic, generic) ▪ Fosinopril, fosinopril HCTZ (Monopril, Monopril HCT generic) ▪ Moexipril +/- HCTZ (Univasc, Uniretic generic) ▪ Perindopril (Aceon, generic) ▪ Quinapril+/- HCTZ (generic) ▪ Trandolapril (Mavik, generic) **ACE Inhibitor/CCB** ▪ Verapamil SR/trandolapril (Tarka, generic) **ARBs** ▪ Candesartan, Candesartan/HCTZ (Atacand, Atacand HCT) ▪ Eprosartan, Eprosartan/ HCTZ (Teveten, Teveten HCT) ▪ Irbesartan, Irbesartan/HCTZ (Avapro, Avalide) ▪ Olmesartan, Olmesartan/HCTZ (Benicar, Benicar HCT) **RAAs/CCB** ▪ Telmisartan/amlodipine (Twynsta) ▪ Olmesartan/amlodipine (Azor) ▪ Valsartan/amlodipine (Exforge) ▪ Valsartan/amlodipine/HCTZ (Exforge HCT) **DRIs** ▪ Aliskiren (Tekturna) ▪ Aliskiren/HCTZ (Tekturna HCT) ▪ Valsartan/aliskiren (Valturna)	▪ Not applicable (no drug designated non-formulary)	Pending 60 days	Step therapy (Automated PA)	**Step-therapy (automated PA)** with the following as the step-preferred drugs: ▪ losartan ±HCTZ ▪ telmisartan ±HCTZ ▪ telmisartan/amlodipine ▪ valsartan ±HCTZ ▪ valsartan/amlodipine ▪ valsartan/amlodipine/ HCTZ Note: telmisartan/amlodipine valsartan/amlodipine & valsartan/amlodipine/HCTZ are step-preferred but not on the BCF

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
Aug 2010	Ophthalmic-1	UF Review	**Antihistamine/Mast Cell Stabilizers** ▪ Olopatadine 0.1% (Patanol)	**Antihistamines** ▪ Emedastine (Emadine) **Mast Cell Stabilizers** ▪ Pemirolast (Alamast) ▪ Nedocromil (Alocril) ▪ Cromolyn (Crolom/Opticrom, generic) ▪ Lodoxamide (Alomide) **Dual Action Antihistamine/Mast Cell Stabilizers** ▪ Bepotastine (Bepreve) ▪ Olopatadine 0.2% (Pataday) ▪ Azelastine (Optivar, generics) ▪ Epinastine (Elestat) **NSAIDs** ▪ Ketorolac 0.4% (Acular LS, generic) ▪ Ketorolac 0.45% (Acuvail) ▪ Ketorolac 0.5% (Acular, generic) ▪ Bromfenac (Xibrom) ▪ Diclofenac (Voltaren, generic) ▪ Flurbiprofen (Ocufen, generics ▪ Nepafenac (Nevanac)	▪ Not applicable (no drug designated non-formulary)	Pending signing of minutes	Not applicable	▪ Ketotifen (Zaditor, generics) is available OTC
May 2010	Antilipidemic-1s	UF Review	▪ Atorvastatin (Lipitor) ▪ Pravastatin(Pravachol, generics) ▪ Simvastatin (Zocor, generics)	▪ Atorvastatin / amlodipine (Caduet) ▪ Ezetimibe (Zetia) ▪ Ezetimibe / simvastatin (Vytorin) ▪ Fluvastatin IR (Lescol) ▪ Fluvastatin ER (Lescol XL) ▪ Lovastatin IR (Mevacor; generics) ▪ Lovastatin ER (Altoprev) ▪ Lovastatin / niacin ER (Advicor) ▪ Niacin IR ▪ Niacin ER (Niaspan) ▪ Rosuvastatin (Crestor) ▪ Simvastatin / niacin ER (Simcor)	▪ Not applicable (no drug designated non-formulary)	Pending 60 days	Step therapy (Automated PA)	Step therapy (automated PA) with generics, or atorvastatin as the preferred agents (note: step- therapy does not apply to ezetimibe or niacin)

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2010	Alpha Blockers for BPH	UF Review	▪ Alfuzosin (Uroxatral) ▪ Tamsulosin (Flomax, generics) ▪ Terazosin (Hytrin; generics)	▪ Doxazosin IR (Cardura; generics)	▪ Silodosin (Rapaflo) ▪ Doxazosin ER (Cardura XL)	Pending 60 days	Step therapy (Automated PA)	Step therapy (automated PA) with tamsulosin (Flomax, generics) or alfuzosin as the preferred agents (note: step- therapy does not apply to terazosin, doxazosin, or doxazosin ER)

ACE: angiotensin converting enzyme
CCB: calcium channel blocker
DRI: direct renin inhibitor
HCTZ: hydrochlorothiazide
NSAID: nonsteroidal anti-inflammatory drug
SR: sustained release

Appendix C—Table of Abbreviations

AC	allergic conjunctivitis
ACE-I	angiotensin converting enzyme inhibitor
AH	Antihistamine
AH/MCS	antihistamines/mast cell stabilizers
ARB	angiotensin receptor blocker
BAK	benzalkonium chloride
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BP	blood pressure
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
CV	Cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
DoD	Department of Defense
DRI	direct renin inhibitor
ECF	Extended Core Formulary
ESI	Express Scripts, Inc
ESRD	end stage renal disease
FCP	Federal Ceiling Price
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HCTZ	Hydrochlorothiazide
IR	immediate release
JNC	Joint National Commission
MARR	Mandatory Agreement for Retail Refunds
MHS	Military Health System
MI	myocardial infarction
mmHg	millimeters mercury
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
NSAIDs	non-steroidal anti-inflammatory drugs
ODT	orally disintegrating tablet
OMB	Office of Management and Budget
Opth-1	Opthalmic-1 drug class
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
QL	quantity limit
SBP	systolic blood pressure
SR	sustained release
TIB	targeted immunomodulatory biologics drug class

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
May 2010

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 12, 2010, and May 13, 2010, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of February minutes**—Dr. Charles Rice, Acting Director, approved the minutes for the February 2010 DoD P&T Committee meeting on May 3, 2010.
2. **Correction to February minutes**—The P&T Committee recommended by consensus the following Factor VIII and Factor IX drugs be returned to formulary status on the Uniform Formulary (UF) upon execution of the DoD Retail Refund Pricing Agreement:

   Human Factor VIII: Humate-P, Monoclate-P

   Recombinant Factor VIII: Helixate FS

   Human Factor IX: MonoNine

   a) ***COMMITTEE ACTION***—The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend the Acting Director, TMA, amend the February 2010 P&T Committee Minutes to reflect the Factor VIII and Factor IX drugs listed, above, have been returned to formulary status on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Narcotic Analgesics—Fentanyl Citrate Transmucosal Soluble Film (Onsolis)

Relative Clinical Effectiveness—Fentanyl citrate transmucosal soluble film (Onsolis) is a pure opioid agonist available in a new transmucosal delivery system. It is FDA-approved for the treatment of breakthrough pain in adults with cancer who are opioid tolerant. Onsolis contains the same active drug (fentanyl) via the same route of administration (oral mucosa) as the UF products Actiq (fentanyl transmucosal lozenge; generics) and Fentora (fentanyl transmucosal tablet). It differs from Actiq and Fentora as fentanyl is delivered through a soluble film that adheres to the mucosal membrane and provides protection from the saliva. The film dissolves completely over 15–30 minutes.

There are no direct comparative clinical trials between Onsolis and the other transmucosal fentanyl products. Onsolis is not bioequivalent with other transmucosal fentanyl products. The safety and tolerability profile for Onsolis appears comparable to other transmucosal fentanyl products. The new delivery system offers more efficient absorption with less swallowing of the drug, which could possibly result in less gastrointestinal (GI) adverse effects. Other potential benefits of the new delivery system include reduced ability for diversion and less risk of dental caries.

Onsolis has a restricted distribution risk evaluation and mitigation strategy (REMS) program that requires enrollment by both the physician and patient, limits dispensing to a single retail pharmacy, and provides delivery of the drug via traceable courier. The FDA is requiring, but has not determined an effective date, for similar REMS programs for Actiq and Fentora.

The narcotic analgesic drug class was last reviewed in February 2007. The clinical evaluation for Onsolis included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) the plausible, yet unproven, benefits of the transmucosal fentanyl buccal film (Onsolis) new delivery system include less GI side effects, less risk of diversion, and less risk of dental caries, compared to other UF transmucosal fentanyl products. The clinical relevance of the proposed advantages is unclear at this time. The FDA-mandated REMS program will ensure use is limited to opioid-tolerant patients.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of fentanyl citrate transmucosal soluble film (Onsolis) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other currently available narcotic analgesics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of the agent. Results from the CMA showed the projected weighted average cost per day for Onsolis is higher than other formulary narcotic analgesics, except the branded drug Actiq.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 0 absent) that fentanyl citrate transmucosal soluble film (Onsolis) is more costly than generic fentanyl products in the narcotic analgesic drug class. In comparison to generics in this class, the P&T Committee determined that the higher daily cost for Onsolis was offset by its unique delivery system and the strict REMS program, which will limit inappropriate prescribing.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 2 opposed, 1 abstained, 0 absent) fentanyl citrate transmucosal soluble film (Onsolis) be designated as formulary on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION***—The P&T Committee considered the BCF status of fentanyl citrate transmucosal soluble film (Onsolis). Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) fentanyl citrate transmucosal soluble film (Onsolis) would not be added to the BCF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

B. Triptans—Sumatriptan Needle-Free Injection (Sumavel DosePro)

Relative Clinical Effectiveness—Sumatriptan needle-free injection (Sumavel DosePro) is a new single-use delivery system for administering sumatriptan subcutaneously. Sumatriptan (Imitrex) is available in oral tablets, a nasal spray, and a traditional needle-containing injection device; all are available in generic formulations. The triptans drug class was last reviewed for UF placement in June 2008. Sumatriptan oral tablets and injection (Imitrex STATdose; generics) are currently included on the BCF.

Sumavel DosePro is FDA-approved for treating migraines and cluster headaches. The sumatriptan dose is delivered by a high pressure burst of nitrogen gas, which propels the drug through the subcutaneous space. Pharmacokinetic studies comparing Sumavel DosePro with Imitrex STATdose demonstrated bioequivalence between the two products. Sumavel DosePro obtained FDA approval via section 505(b)(2) of the Federal Food, Drug, and Cosmetic (FDC) Act using data submitted from the original Imitrex STATdose submission. Thus, there are no clinical trials with Sumavel DosePro that measure efficacy for providing pain relief from migraine headaches. Following administration, initially there is a higher incidence of bleeding, swelling, and bruising with Sumavel Dose Pro than with Imitrex STATdose; these adverse effects dissipate, and show no difference in severity with Imitrex STATdose 8 hours after administration. Potential benefits of Sumavel DosePro compared to sumatriptan needle-containing injection include that the device is easy to use, it provides an alternative injection option to patients with severe needle phobia, and it does not require special biohazard disposal (e.g., disposal in household refuse).

The clinical evaluation for Sumavel DosePro included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that although sumatriptan needle-free injection (Sumavel DosePro) is easy to use, particularly for patients with dexterity issues, and can be disposed of without special precautions, it does not have a significant, clinically relevant therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to the existing UF product, sumatriptan needle-containing injection.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of sumatriptan needle-free injection (Sumavel DosePro) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other non-oral sumatriptan formulations included in the triptans drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Sumavel DosePro relative to other non-oral UF sumatriptan agents. Results from the CMA showed the projected weighted average cost per day for Sumavel DosePro is higher than other non-oral sumatriptan formulary agents, with the exception of the Imitrex STATdose proprietary formulation.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 0 absent) that sumatriptan needle-free injection (Sumavel DosePro) is more costly compared to current UF agents except the Imitrex STATdose proprietary formulation.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 0 opposed, 1 abstained, 0 absent) sumatriptan needle-free injection (Sumavel DosePro) be designated nonformulary (NF) on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of sumatriptan needle-free injection (Sumavel DosePro) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Sumavel DosePro. (See Appendix B for full MN criteria).

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent)
   1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at Military Treatment Facilities (MTFs) no later than a 60-day

implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UF DRUG CLASS REVIEWS

A. Antilipidemic-1s (LIP-1s)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the agents in the Antilipidemic-1s (LIP-1s) drug class. This class is currently ranked number one in the Military Health System (MHS), with drug class expenditures exceeding $480 million annually. The class was last reviewed in August 2006. The individual drugs included in the LIP-1s class are listed, below:

Statins: atorvastatin (Lipitor), amlodipine/atorvastatin (Caduet), fluvastatin (Lescol), fluvastatin extended release (ER; Lescol XL), lovastatin (Mevacor, generics), lovastatin ER (Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor), simvastatin (Zocor, generics), and ezetimibe/simvastatin (Vytorin)

Statin combination products and add-on therapies: niacin ER (Niaspan), lovastatin/niacin ER (Advicor), simvastatin/niacin ER (SIMCOR), and ezetimibe (Zetia)

The current BCF agents are pravastatin, simvastatin, niacin ER (Niaspan), and ezetimibe/simvastatin (Vytorin). The NF agents are atorvastatin/amlodipine (Caduet) and rosuvastatin (Crestor). The remaining drugs are classified as UF agents. Generic formulations of simvastatin, pravastatin, and lovastatin are now marketed. Generic formulations of atorvastatin are expected in late 2011.

Relative Clinical Effectiveness Conclusion—The Committee recommended (14 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for the LIP-1s:

1. Across equipotent doses, the statins achieve a similar percentage reduction in low-density lipoprotein (LDL), and a similar percentage increase in high-density lipoprotein (HDL).
2. All statins show a plateau and drop-off in ability to raise HDL at increasing doses.
3. Doubling the dose of a statin provides only an additional 4% to 7% reduction in LDL and 3% to 6 % reduction in non-HDL.
4. There is a strong correlation between the change in LDL and C-reactive protein (CRP). CRP appears to be a strong predictor of coronary heart disease (CHD). It is unclear what emphasis the upcoming National Heart and Lung Blood Institute Adult Treatment Panel (ATP) IV guidelines will place on CRP in managing patients with hypercholesterolemia.
5. A 1:1 log-linear relationship exists between lowering LDL and non-HDL and reduced relative risk of CHD. In one mortality study, non-HDL was a stronger predictor of CHD risk than LDL.
6. With respect to the low-to-moderate intensity statins (statins able to reduce LDL levels by $\leq 45\%$):
   - The results of one meta-analysis show Lipitor, pravastatin, and simvastatin have similar effects in providing long-term cardiovascular (CV) prevention (e.g., reducing all-cause deaths, major coronary events, CV death, and major cerebrovascular events).
   - There are fewer trials published for lovastatin and fluvastatin, but positive outcomes are still shown.
   - Simvastatin at doses ≤ 40 mg will remain the DoD-preferred statin.
7. The high-intensity statins (those statins able to reduce LDL levels by >45%) include Lipitor 40 and 80 mg; Vytorin 10/20, 10/40, and 10/80 mg; Crestor 10, 20, and 40 mg; and simvastatin 80 mg.
8. In trials assessing the primary prevention of CHD, statins do not appear to decrease the risk of all-cause mortality. At a dose of 20 mg, Crestor showed a decreased risk of all-cause mortality in the JUPITER trial. The benefit of Crestor in this trial was limited to patients with CRP> 2 and an additional CHD risk factor besides age. When used in the primary prevention of CHD, statins in general decrease the risk of CV events by 22% to 30%.

9. In trials assessing the secondary prevention of CHD, statins decrease the risk of mortality and the risk of major CV events 21% to 23%. Similar benefits are conferred among patients with or without diabetes. When used in acute coronary syndrome, Lipitor 80 mg decreases the risk of a second event by 16% to 19%. There are no studies with Crestor assessing the secondary prevention of CHD.
10. Vytorin provides added efficacy in terms of LDL lowering, but still lacks clinical outcomes data showing a reduction in CV events. Positive benefits in reducing CV events have been shown with the simvastatin component of Vytorin in The Heart Protection Study and The Scandinavian Simvastatin Survival Study trials.
11. Zetia lowers LDL 15%–20% by a mechanism distinct from that of the statins.
12. Niaspan lowers LDL 5%–15%. However, Niaspan is required in the MHS, as its primary benefit is to raise HDL by 25%.
13. Since the 2006 review, there is no new compelling data for Advicor, SIMCOR, Caduet, Altoprev, or Lescol XL to change the original conclusion that these drugs do not offer additional clinical benefits over the other LIP-1s. These drugs have low utilization in the MHS.
14. With regard to safety, there is no evidence that increases in liver function tests or minor adverse events (gastrointestinal disturbances, headaches, rash, itching) are less likely to occur with one statin versus another; these adverse effects are dose-related.
15. Concerns of proteinuria remain with Crestor 40 mg, but the clinical significance of this effect is unknown.
16. The risk of statin-related myotoxicity increases with increasing dosages. There is no evidence that one statin is less likely to cause myotoxicity than another. The FDA recently updated the labeling for simvastatin 80 mg, warning of the risk of myotoxicity. The overall incidence of rhabdomyolysis is rare with all statins.
17. There is no conclusive data yet to suggest that statin therapy is associated with cognitive decline, behavioral defects, or cancer. However, there is evidence to suggest an increased risk of new onset diabetes with statin therapy (JUPITER trial and Lancet 2010 meta-analysis). The clinical implications of this finding are still unclear.

18. Fluvastatin, pitavastatin (a new statin not yet marketed), pravastatin, and Crestor do not interact with CYP 3A4 and have more favorable drug-drug interaction profiles than the other statins. Pravastatin is renally metabolized and bypasses the CYP 450 system entirely.
19. The Pharmacy Outcomes Research Team (PORT) analyzed LIP-1s utilization in the MHS during a 7-month period between August 1, 2009, and March 31, 2010. Overall, approximately 1.4 million DoD beneficiaries receive lipid-lowering therapies and about 1.2 million DoD beneficiaries receive statins. The percentage of the study group classified as new statin users was 7%. Women comprised 51% of the entire study group; the mean patient age was 42.4 years (standard deviation 11.8 years).

    The majority of use is statin monotherapy (882,000 patients). The most common add-on therapy is ezetimibe (194,000), followed by fibrates (123,000) and niacin (57,000). Zetia is frequently prescribed as Vytorin (73%); only 27% of the study group received Zetia with a statin other than simvastatin. Most niacin is given separately (74%), with only 6,819 patients receiving SIMCOR or Advicor.

    About 29% of all patients receiving statin monotherapy or a statin and Zetia are receiving high-intensity statins (statins able to reduce LDL levels by >45%); 17% of this group is receiving a high-intensity statin alone; 11% are receiving a high-intensity statin plus Zetia. The most common triple therapy is a statin and Zetia and niacin (12,000). Overall, about 73,000 patients receive some combination targeting LDL and HDL/triglycerides.
20. To meet the clinical needs of the majority of MHS patients, the UF must include the low-to-moderate intensity statins simvastatin and pravastatin, and at least one high-intensity statin.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the LIP-ls in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Statins: A series of cost-effectiveness analyses (CEAs) and budget impact analysis (BIAs) were used to determine the relative cost-effectiveness of agents in the class.

Four separate cost-effectiveness models were constructed in the analyses of low-to-moderate statins (statins able to reduce LDL levels by ≤ 45%) and high-intensity statins (statins able to reduce LDL levels by >45%). Analyses were based on direct and indirect comparisons of relevant trial data.

1. The Annual Cost per 1% LDL Decrease Model compared the cost-effectiveness of the high % LDL-lowering agents based on annual cost per 1% LDL reduction using a decision analytical model.
2. The Annual Cost per Patient Treated to Goal Model compared the cost-effectiveness of these agents based on annual cost per patient successfully treated to ATP III National Cholesterol Education Program goal using a decision analytical model.
3. The Annual Cost per 1% Non-HDL Decrease Model compared the cost-effectiveness of the high % non-HDL lowering agents based on annual cost per 1% non-HDL reduction using a decision analytical model.
4. The Annual Cost per 1% HDL-increase Model compared the cost-effectiveness of the high % HDL-increasing agents based on annual cost per 1% HDL increase using a decision analytical model.

Statin combination products and add-on therapies: CMA and BIA were used to evaluate the cost-effectiveness of the statin combination products and add-on therapies.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

Statins (13 for, 0 opposed, 1 abstained, 1 absent)**:**

1. For the low-to-moderate % LDL-lowering agents (≤ 45% LDL reduction) evaluated: simvastatin (10, 20, and 40 mg), Lipitor 10 and 20 mg, and all strengths of pravastatin, the cost-effectiveness of the agents in this class were evaluated using each of the decision analytic models described, above. In pharmacoeconomic terms, simvastatin was considered to be dominant at all equipotent strengths, in terms of cost per LDL reduction, cost per LDL goal attainment, cost per non-HDL reduction, and cost per HDL increase. CEA results showed simvastatin was located along the cost efficiency frontier and considered to be the optimal agent.

Note: Based on low utilization and conclusions presented at the August 2006 P&T Committee Meeting, the following agents were not evaluated in the model(s): simvastatin 5 mg, Crestor 5 mg, ezetimibe/simvastatin (Vytorin) 10/10 mg, fluvastatin IR, fluvastatin ER, lovastatin IR, and lovastatin ER were not included in the CEA).

2. For the high-intensity % LDL-lowering agents (> 45% LDL reduction) evaluated: Lipitor 40 and 80 mg, Crestor 10, 20, and 40 mg, simvastatin/ezetimibe (Vytorin) 10/20, 10/40, 10/80 mg, and simvastatin 80 mg, the cost-effectiveness of the agents in this class were evaluated using each of the decision analytic models described, above. In pharmacoeconomic terms, the results of the first three cost-effectiveness analyses showed Lipitor 40 and 80 mg to be the overall most cost-effective high-intensity agent(s), in terms of cost per % LDL reduction, cost per % LDL goal attainment, and cost per % non-HDL reduction. Crestor 40 mg was more effective but considerably more costly compared to Lipitor at equipotent doses, but not more effective nor less costly than the equipotent dosage of ezetimibe/simvastatin (Vytorin) 10/80 mg. CEA determined Vytorin was not dominant in cost per outcome compared to Lipitor. From a price per % LDL-reduction perspective, Lipitor (all strengths) was more cost-effective than Vytorin. CEA results showed Lipitor 40 and 80mg was located along the cost efficiency frontier and considered to be the optimal agent(s).

3. BIA was used to assess the potential impact of cost scenarios where selected LIP-1s were designated formulary or nonformulary on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. Results from the BIA for LIP-1s revealed that the scenarios placing Lipitor at all strengths on the BCF and as the step-preferred product in front of a step-therapy requirement and placing all generic agents in front of a step-therapy requirement were the most cost-effective scenarios.

4. The results of the BIA showed that Lipitor was less costly than the other brand agents Crestor and Vytorin in all scenarios evaluated. All scenarios placing Lipitor in the step-preferred position were less costly than all nonstep-scenarios and all other scenarios involving multiple step-preferred branded agents.

Statin combination products and add-on therapies (14 for, 0 opposed, 0 abstained, 1 absent):

1. The CMA results revealed that SIMCOR was the most cost-effective add-on product, based on an analysis of the cost per day of therapy. Cost per day of therapy was calculated using cost per tablet adjusted by daily average consumption (DACON) rates for SIMCOR, Niaspan, Advicor, and Zetia.
2. BIA was used to assess the potential impact of cost scenarios where selected statin combination products and add-on agents were designated formulary or nonformulary on the UF. Scenarios evaluating the impact of designating agents on the BCF were also considered. Results from the BIA revealed the most cost-effective scenario overall to add Niaspan on the BCF and UF, add Zetia on the UF, and designate SIMCOR and Advicor NF. However, designating SIMCOR NF may result in increased usage of Niaspan and increase overall costs. Sensitivity analyses show no individual scenario was dominant after considering the margin for error present in all cost projections. Therefore, the cost avoidance of the aforementioned most cost-effective scenario was within the margin of error.

a) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

(1) Ezetimibe/simvastatin (Vytorin), Atorvastatin (Lipitor), simvastatin (Zocor, generics), fluvastatin (Lescol), fluvastatin ER (Lescol XL), lovastatin (Mevacor, generics), lovastatin ER (Altoprev) and pravastatin (Pravachol, generics) remain classified as formulary on the UF; and that atorvastatin/amlodipine (Caduet) and rosuvastatin (Crestor) be designated formulary agents on the UF, with prior authorization (PA) for the LIP-1s drug class requiring a trial of atorvastatin (Lipitor) and the generic formulations of simvastatin or pravastatin for new patients (12 for, 0 opposed, 2 abstained, 1 absent);

(2) Ezetimibe (Zetia), niacin ER (Niaspan), lovastatin/niacin ER (Advicor), and simvastatin/niacin ER (SIMCOR) remain designated as UF; (13 for, 0 opposed, 1 abstained, 1 absent);

(3) As a result of the above recommendations, there are no LIP-1s designated as nonformulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

b) ***COMMI TTEE ACTION: PA CRITERIA***—The Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) the following PA criteria should apply to the LIP-1s other than generics and Lipitor. Coverage would be approved if the patient met any of the following criteria:

(1) Automated PA criteria:

(a) The patient has received a prescription for a preferred agent targeting similar LDL reduction at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) PA criteria, if automated criteria are not met:

(a) The patient has tried the preferred agent and was unable to tolerate treatment due to adverse effects.

(b) The patient is taking a concurrent drug that is metabolized by CYP3A4.

(c) The patient requires ≥55% LDL lowering.

(d) The patient requires primary prevention with rosuvastatin (Crestor) and is not able to take atorvastatin (Lipitor).

Acting Director, TMA, Decision: ☑ *Approved* ☐ *Disapproved*

Approved, but modified as follows:

c) ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries

affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows

d) ***COMMI TTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended:

(1) Simvastatin (Zocor, generics) and pravastatin (Pravachol, generics) remain BCF; atorvastatin (Lipitor) be added to the BCF; and, ezetimibe/simvastatin (Vytorin) be removed from the BCF (11 for, 0 opposed, 2 abstained, 2 absent);

(2) Niacin ER (Niaspan) remain BCF (13 for, 0 opposed, 1 abstained, 1 absent).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Alpha Blockers for Benign Prostatic Hyperplasia (BPH)

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the alpha blockers used for BPH currently marketed in the United States. The class is comprised of three non-uroselective agents: terazosin (Hytrin, generics), doxazosin immediate release (IR; Cardura; generics), and doxazosin ER (Cardura XL); and three uroselective agents: alfuzosin (Uroxatral), tamsulosin (Flomax) and silodosin (Rapaflo). Generic formulations of tamsulosin were launched in March 2010. The BPH alpha blocker drug class was first reviewed in August 2005 and reviewed again in November 2007. The newest agent, Rapaflo, was reviewed in August 2009. Current annual expenditures for the BPH alpha blockers are $52 million.

There is an existing automated PA process for the uroselective alpha blockers, which requires a trial of Uroxatral as initial therapy. All the alpha blockers are FDA-approved for treating BPH. The clinical evaluation for the BPH alpha blockers included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding the BPH alpha blockers:

1. There are limited head-to-head trials comparing the BPH alpha blockers; the available placebo-controlled trials and meta-analyses were reviewed. Although all the alpha blockers are superior to placebo, variability in study design and demographics preclude the ability to designate one agent as clinically superior.
2. Based on randomized placebo-controlled trials, terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin produce clinically significant and comparable symptom improvements when compared to placebo.
3. Uroselective agents are well tolerated, with a few differences in safety considerations.
4. Uroselective agents appear to be better tolerated than non-uroselective agents, as measured by withdrawals due to adverse events and discontinuation of therapy.
5. Non-uroselective alpha blockers exhibit a higher rate of vasodilatory adverse effects relative to uroselective alpha blockers
6. All agents have similar warnings regarding intraoperative floppy iris syndrome.
7. The PORT analyzed the rejected claims attributable to the existing automated PA process (step-therapy edit) for the BPH alpha blockers from April 16, 2008, to December 31, 2009.
    a) Over the study period, 154,691 patients received uroselective alpha blockers for BPH in the retail or mail points of service; 43% of the patients encountered the step-therapy edit reject. Step therapy was highly effective at causing switches to preferred products; 81% of the patients who received a selective alpha blocker received the preferred product, alfuzosin, within 90 days. However, a substantial percentage of patients did not receive an alpha blocker within 90 days; 30% of patients did not receive a selective alpha blocker and 26% did not receive any alpha blocker (selective or non-selective).
    b) About 7% of the patients affected by the step therapy edit were female. Results for the women were similar to the overall results: 81% of women receiving a selective alpha blocker were switched to alfuzosin. However, the majority of women (64%) encountering the reject did not receive a selective alpha blocker within 90 days.
    c) When the alpha blocker step-therapy results were compared to previous analyses of UF drugs with step edits, similar results were noted. The percentages for those patients who did not receive a prescription after the step-edit reject were 35% in the newer sedative hypnotics class, and 31%

in the proton pump inhibitor class, versus 26%–30% in the alpha blocker class.

8. A review of the clinical literature since the previous UF reviews did not add substantial new information or support changes in clinical practice.
9. Terazosin, doxazosin, and doxazosin ER have a low degree of therapeutic interchangeability with alfuzosin, tamsulosin, and silodosin in terms of safety and tolerability, due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective alpha blockers.
10. Alfuzosin, tamsulosin, and silodosin have a high degree of therapeutic interchangeability; any of these drugs could be expected to meet the needs of the majority of MHS BPH patients requiring an uroselective agent.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the alpha blockers used for BPH in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA and BIA were used to evaluate the cost-effectiveness of the BPH alpha blockers. Currently, there is a national shortage of doxazosin, resulting in a higher price for some dosage strengths.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) the following:

1. CMA results for the non-uroselective agents revealed that generic terazosin and generic doxazosin IR were the most cost-effective agents based on the weighted average cost per day of therapy.

2. CMA results for the uroselective agents revealed that generic tamsulosin was the most cost-effective agent and Rapaflo (silodosin) was the least cost-effective agent based on the weighted average cost per day of therapy.

3. BIA results revealed the scenario that placed generic tamsulosin alone in front of a step on the UF and the scenario that included generic tamsulosin and Uroxatral (alfuzosin) on the UF in front of a step were the most cost effective.

a) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and

relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend (11 for, 3 opposed, 1 abstained, 0 absent) that:

(1) tamsulosin (generic Flomax) and alfuzosin (Uroxatral) be designated as the uroselective UF alpha blockers; terazosin (Hytrin, generics) and doxazosin IR (Cardura) be maintained as the non-uroselective UF alpha blockers;

(2) silodosin (Rapaflo) remain classified as NF with a PA requiring a trial of alfuzosin or generic tamsulosin for new patients; and

(3) doxazosin ER (Cardura XL) be classified as the NF non-uroselective alpha blocker for BPH.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

b) ***COMMI TTEE ACTION: PA CRITERIA***—The automated PA (step therapy) currently in effect requires alfuzosin (Uroxatral) before other NF alpha blockers for BPH, unless there is therapeutic failure, intolerance, or hypersensitivity. The automated PA criteria will now include generic tamsulosin as a preferred BPH alpha blocker, along with alfuzosin (Uroxatral). The P&T Committee voted (13 for, 0 opposed, 2 abstained, 0 absent) to recommend the PA criteria outlined, below, should apply to silodosin (Rapaflo); there is no change to the criteria for silodosin previously in effect. Coverage would be approved if the patient met any of the following criteria:

(1) Automated PA criteria:

(a) The patient has received a prescription for either silodosin (Rapaflo), tamsulosin (generic Flomax), or alfuzosin (Uroxatral) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) PA criteria if automated criteria are not met:

(a) The patient has tried alfuzosin (Uroxatral) or tamsulosin and had an inadequate response or was unable to tolerate treatment due to adverse effects.

(b) Treatment with alfuzosin (Uroxatral) or tamsulosin is contraindicated.

(c) The patient requires an alpha blocker that can be crushed and sprinkled on food.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

c) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of the alpha blockers for BPH, and the conditions for establishing MN for a NF medication, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for the uroselective alpha blocker silodosin (Rapaflo), and recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for the non-uroselective alpha blocker doxazosin ER (Cardura XL). (See Appendix B for full MN criteria.)

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

d) ***COMMI TTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

e) ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 1 opposed, 1 abstained, 0 absent) to retain alfuzosin (Uroxatral) and terazosin (Hytrin) on the BCF, and add tamsulosin (generic Flomax) to the BCF.

Acting Director, TMA, Decision: ☐ Approved ☐ Disapproved

Approved, but modified as follows:

V. UTILIZATION MANAGEMENT

A. PA Requirement for Quinine—Quinine sulfate has been used off-label for years to treat nocturnal leg cramps. The only quinine product approved by the FDA (marketed under the trade name Qualaquin) is only approved for treating malaria; however, the FDA recognizes that the majority of its use is for leg cramps.

In the MHS, between April 1, 2009, and March 31, 2010, over 10,300 patients were prescribed quinine, with over 70% of the prescriptions dispensed from the retail network. The majority of patients receiving quinine sulfate prescriptions are older than 45 years. The current MHS usage is 80% lower than that reported in a DoD P&T Committee analysis from 2004. Results from an analysis of MHS quinine prescriptions during fiscal year 2009 found that out of 11,341 patients, 24% had one or more ICD-9 codes associated with leg cramps and 0.1% had ICD-9 codes associated with malaria; 76% of patients did not have ICD-9 codes for either malaria or leg cramps.

Meta-analyses and professional guidelines conclude that quinine is likely effective in reducing the frequency of muscle cramps, but the magnitude of benefit is small. No drug is currently FDA-approved for leg cramps, and there are no clearly effective pharmacological or nonpharmacological alternatives. A 2006 post-marketing FDA

surveillance study reported that since 1969 there have been 665 reports of adverse events involving quinine sulfate, including 93 deaths. Serious adverse events reported with quinine sulfate include thrombocytopenia, hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS-TTP), chronic renal impairment associated with HUS-TTP, hypersensitivity reactions, and QT prolongation. The product labeling for Qualaquin was updated in 2009 to state that the risk associated with quinine sulfate when used for nocturnal leg cramps outweighs any potential benefit.

1. ***COMMITTEE ACTION: PA***—Due to continued safety concerns and FDA advisories recommending against use of quinine sulfate for leg cramps, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) a PA be required for quinine sulfate (Qualaquin) that limits use to the FDA-approved indication of malaria. The PA would apply to both existing and new users of quinine sulfate.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: PA IMPLEMENTATION***—The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend the quinine sulfate PA should have an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at the MTFs, no later than a 60-day implementation date. The implementation period will begin immediately following the approval by the Director, TMA.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

VI. BASIC CORE FORMULARY ISSUES

A. Fluticasone proprionate nasal spray (Flonase, generics)—BCF Deletion

The Nasal Allergy Drugs, which include the nasal corticosteroids, were last reviewed in November 2008. Generic fluticasone propionate nasal spray (Flonase) was selected as the BCF nasal corticosteroid. Supplies of both generic and branded fluticasone propionate nasal spray are limited, due to manufacturing plant closures by the FDA and exit of the proprietary manufacturer from the market. The result is an increase in price from the two remaining generic manufacturers. It is unknown when additional supplies will be available. Due to the aforementioned developments, the P&T Committee recommended deleting fluticasone propionate nasal spray from the BCF. Fluticasone propionate nasal spray will remain on the UF. MTFs are encouraged to provide an alternative nasal corticosteroid in the interim, to meet local needs.

1. ***COMMITTEE ACTION: BCF DELETION***—The Committee voted (13 for, 1 opposed, 1 abstained, 0 absent) to remove fluticasone propionate nasal spray (Flonase, generics) from the BCF immediately upon signing of the May 2010 DoD P&T Committee minutes; it will remain formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Department of Veterans Affairs (VA)/DoD Joint Contracting Initiatives—Non-Basal Insulins BCF Addition

The P&T Committee was briefed regarding the VA National Acquisition Center contract for the non-basal insulin, including insulin aspart (Novolog) and 70% insulin aspart protamine suspension/30% insulin aspart (Novolog Mix 70/30). The insulin aspart (Novolog) vials are currently on the BCF. As part of the new contract, the insulin aspart pen injection devices (Novolog FlexPen) and insulin aspart PenFill cartridges (Novolog PenFill) are now cost-effective and have a similar price/mL as the vials. Likewise the 70% insulin aspart protamine suspension/30% insulin aspart pen injection device (Novolog Mix 70/30 FlexPen) is now similarly priced to the vials.

1. ***COMMITTEE ACTION: BCF ADDITION***—The Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend adding the insulin aspart pen injection device (Novolog FlexPen), the insulin aspart PenFill cartridges (Novolog PenFill), and the 70% insulin aspart protamine suspension/30% insulin

aspart pen injection device (Novolog Mix 70/30 FlexPen) to the BCF, immediately upon signing of the May 2010 DoD P&T Committee minutes.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VII. ITEMS FOR INFORMATION

A. **Pharmacy Outcomes Research Team (PORT)**—The PORT briefed the P&T Committee on their completed, ongoing and future research projects.

VIII. NATIONAL DEFENSE AUTHORIZATION ACT, SECTION 703—INCLUSION OF TRICARE RETAIL PHARMACY PROGRAM IN FEDERAL PROCUREMENT OF PHARMACEUTICALS UPDATE

The P&T Committee reviewed drugs that have been established on a DoD Retail Refund Pricing Agreement; these drugs are now compliant with Fiscal Year 2008 National Defense Authorization Act, Section 703. By law, these drugs were designated NF on the UF and subject to pre-authorization prior to use in the retail point of service (POS) and MN in MTFs. These drugs are now eligible to return to their previous formulary status without a pre-authorization requirement. Drugs with pricing agreements were systematically classified according to therapeutic and pharmacologic lines. The classification system was based on the American Hospital Formulary System Classification and First Data Bank classification.

A. ***COMMITTEE ACTION: DRUGS RETURNED TO UF STATUS***—The P&T Committee recommended by consensus the drugs listed in Appendix C return to formulary status on the UF. See Appendix C for the full list of affected medications.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: DRUGS MAINTAINING NF STATUS BUT NOT SUBJECT TO PREAUTHORIZATION***—The P&T Committee recommended by consensus the following drugs maintain NF status and not be subject to PA:

Daytrana, Kapidex, Saizen, Azor, Welchol, Cardene SR, and Vyvanse

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. CLASS OVERVIEWS

The Antidiabetic Drug Class overview was presented to the P&T Committee. The Antidiabetic Drug Class is comprised of the sulfonylureas, sulfonylurea combinations, alpha glycoside agonists, amylin analogs, biguanides, meglitinides, thiazolidinediones, glucose-like-peptide 1 agents, and the dipeptidyl peptidase-4 (DPP-4) inhibitors. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost-effectiveness models. The clinical and economic analyses of this class will be presented at an upcoming meeting.

IX. ADJOURNMENT

The meeting adjourned at 1700 hours on May 12, 2010, and at 1100 hours on May 13, 2009. The next meeting will be in August 2010.

Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria

Appendix C—National Defense Authorization Act, Section 703 Affected Medications

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Appendix E—Table of Abbreviations

SUBMITTED BY:

CDR James Ellzy, MC, USN
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Dr. Charles L. Rice
Acting Director

23 July 2010
(Date)

Appendix A—Attendance

Voting Members Present	
CDR James Ellzy, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center, (Recorder)
Lt Col Thom Bacon, BSC *for Col Everett McAllister, BSC*	Deputy Director, Pharmaceutical Operations Directorate
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
CAPT David Tanen, MC	Navy, Physician at Large
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
Lt Col Brian Crownover, MC	Air Force, Physician at Large
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician, Alternate
LTC Bruce Lovins, MC	Army, Family Practice Physician, Alternate
COL Ted Cieslak, MC	Army, Physician at Large
COL Peter Bulatao *for COL Carole Labadie, MSC*	Army, Pharmacy Officer, Alternate
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Assistant General Counsel, TMA
CDR Michele Hupp, MSC	Defense Medical Standardization Board
Guests	
Lt Col Kirk Stocker	AFMOA
Capt Julie Meek	Air Force Pharmacy Resident
Dr. Barbara Vize	United States Public Health Service/ Indian Health Service
Dr. David Trang	University of Incarnate Word Pharmacy School
Dr. Bernadette Heron	VA PBM
Dr. Annabel Schumaker	Lackland AFB

Appendix A—Attendance (continued)

Others Present	
COL Cynthia Clagett	DoD Pharmacoeconomic Center
LCDR Joe Lawrence	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
CPT Brian Haney, MC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Roger Potyk	DoD Pharmacy Outcomes Research Team contractor
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor
Dr. Brian Beck	DoD Pharmacy Operations Center contractor

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Silodosin (Rapaflo) **Alpha Blockers for BPH**	• Use of the formulary agent is contraindicated. • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • There is no alternative formulary agent available, and the patient requires a drug that can be crushed or sprinkled on food.
Doxazosin ER (Cardura XL) **Alpha Blockers for BPH**	• The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
Sumatriptan needle-free injection (Sumavel) **Triptans**	• No alternative formulary agent available for patients with needle phobia or those with dexterity issues who cannot manipulate the sumatriptan injection (Imitrex STATdose, generics).

Appendix C—National Defense Authorization Act, Section 703 Affected Medications

Product Name	Subclass	Manufacturer
DEPAKENE	Anticonvulsants	ABBOTT LABS
OMNICEF	3rd gen cephalosporins	ABBOTT LABS
PCE	Macrolide	ABBOTT LABS
DIPENTUM	Medications for inflammatory bowel disease	ALAVEN PHARMA
KADIAN	Higher potency single analgesic agents	ALPHARMA BPD
ALLEGRA	2nd gen antihistamines & combos	AVENTIS PHARM
CYTOXAN	Alkylating agents	BMS ONCO/IMMUN
CATAPRES	Sympatholytics	BOEHRINGER ING.
EVOXAC	Parasympathetic agents	DAIICHI SANKYO
FLOXIN	Otic medications, anti-infective	DAIICHI SANKYO
BANZEL	Anticonvulsants/antimania medications	EISAI INC.
FRAGMIN	Anticoagulants	EISAI INC.
SALAGEN	Parasympathetic agents	EISAI INC.
ZONEGRAN	Anticonvulsants	EISAI INC.
CETROTIDE	LHRH (GNRH) antagonist, pituitary suppressant age	EMD SERONO, INC
LUVERIS	Luteinizing hormones	EMD SERONO, INC
SEROSTIM	Growth hormone	EMD SERONO, INC
ZORBTIVE	Growth hormone	EMD SERONO, INC
BRAVELLE	FSH/LH fertility agents	FERRING PH INC
ENDOMETRIN	Pregnancy facilitating/maintaining agent	FERRING PH INC
REPRONEX	FSH/LH fertility agents	FERRING PH INC
LAMICTAL ODT	Anticonvulsants/antimania medications	GLAXOSMITHKLINE
LAMICTAL ODT (BLUE)	Anticonvulsants/antimania medications	GLAXOSMITHKLINE
LAMICTAL ODT (GREEN)	Anticonvulsants/antimania medications	GLAXOSMITHKLINE
LAMICTAL ODT (ORANGE	Anticonvulsants/antimania medications	GLAXOSMITHKLINE
LAMICTAL XR	Anticonvulsants/antimania medications	GLAXOSMITHKLINE
DERMA-SMOOTHE-FS	Topical corticosteroids	HILL DERM
PERANEX HC	Topical corticosteroids/immune modulators	KENWOOD LAB
FLEXERIL	Skeletal muscle relaxants	McNEIL CONS
UROCIT-K	Urinary agent	MISSION
LITHOSTAT	Ammonia inhibitors	MISSION PHARM
TINDAMAX	Antiprotozoal	MISSION PHARM
LINDANE	Misc topical anti-infectives	MORTON GROVE PH
ERGOLOID MESYLATE	Misc cardiovascular medications	MUTUAL PHARM CO
KERAFOAM	Keratolytics	ONSET THERAPEUT
OPTASE	Misc topical agents	ONSET THERAPEUT
SALKERA	Keratolytics	ONSET THERAPEUT
PROCRIT	RBC stimulants	ORTHO BIOTECH
METANX	Vitamin B preparations	PAN AMERICAN
DILANTIN	Anticonvulsants/antimania medications	PFIZER US PHARM
OGEN	Estrogens & estrogen/androgen combos	PHARMACIA/UPJOHN
TENEX	Sympatholytics	PROMIUS PHARMA
MS CONTIN	Higher potency single analgesic agents	PURDUE PHARMA L
DORAL	Sedative/hypnotics II	QUESTCOR
RIOMET	Biguanides	RANBAXY BRAND D
ANAPROX	NSAIDs	ROCHE LABS
ANAPROX DS	NSAIDs	ROCHE LABS

Appendix C—National Defense Authorization Act, Section 703 Affected Medications (continued)

Product Name	Subclass	Manufacturer
KLONOPIN	Anticonvulsants	ROCHE LABS
KYTRIL	5HT3 antiemetics	ROCHE LABS
VALIUM	Anxiolytics	ROCHE LABS
VESANOID	Misc antineoplastics	ROCHE LABS
VIMPAT	Anticonvulsants/antimania medications	SCHWARZ PHARMA
AGRYLIN	Platelet reducing agents	SHIRE US INC.
CARBATROL	Anticonvulsants	SHIRE US INC.
FOSRENOL	Phosphate binders	SHIRE US INC.
LIALDA	Medications for inflammatory bowel disease	SHIRE US INC.
PENTASA	Medications for inflammatory bowel disease	SHIRE US INC.
PROAMATINE	Adrenergic vasopressors	SHIRE US INC.
NEOBENZ MICRO	Keratolytics	SKINMEDICA
ELDEPRYL	Parkinson's medications	SOMERSET PHARM
LOCOID	Topical corticosteroids	TRIAX PHARMACEU
MINOCIN	tetracyclines	TRIAX PHARMACEU
SULFAMYLON	Topical sulfonamides	UDL
ANDROID	Androgens/anabolic steroids	VALEANT
OXSORALEN	Hyperpigmentation agents	VALEANT
TESTRED	Androgens/anabolic steroids	VALEANT
QUIXIN	Ophthalmic antibiotics, quinolones	VISTAKON PHARMA
MUSE	Prostaglandins for ED	VIVUS
FIORICET	Analgesic combos	WATSON PHARMA
MYAMBUTOL	Antitubercular medications	X-GEN PHARMACEU

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
May 2010	Antilipidemic -1s	~~UF~~ Review	▪ Atorvastatin (Lipitor) ▪ Pravastatin(Pravachol, generics) ▪ Simvastatin (Zocor, generics)	▪ Atorvastatin / amlodipine (Caduet) ▪ Ezetimibe (Zetia) ▪ Ezetimibe / simvastatin (Vytorin) ▪ Fluvastatin IR (Lescol) ▪ Fluvastatin ER (Lescol XL) ▪ Lovastatin IR (Mevacor; generics) ▪ Lovastatin ER (Altoprev) ▪ Lovastatin / niacin ER (Advicor) ▪ Niacin IR ▪ Niacin ER (Niaspan) ▪ Rosuvastatin (Crestor) ▪ Simvastatin / niacin ER (Simcor)	▪ Not applicable (no drug designated non-formulary)	Pending 60 days	Step therapy (Automated PA)	August 2006	Step therapy (automated PA) with generics, or atorvastatin as the preferred agents. (note: step therapy does not apply to ezetimibe or niacin)
May 2010	Alpha Blockers for BPH	UF Review	▪ Alfuzosin (Uroxatral) ▪ Tamsulosin (Flomax, generics) ▪ Terazosin (Hytrin; generics)	▪ Doxazosin IR (Cardura; generics)	▪ Silodosin (Rapaflo) ▪ Doxazosin ER (Cardura XL)	Pending 60 days	Step therapy (Automated PA)	August 2009 (silodosin); Nov 2007; Aug 2005	Step therapy (automated PA) with tamsulosin or alfuzosin as the preferred agents. (note: step therapy does not apply to terazosin, doxazosin, or doxazosin ER)
May 2010	Triptans	New Drug Sumatriptan needle-free injection (Sumavel DosePro)	▪ Rizatriptan (Maxalt; Maxalt MLT) ▪ Sumatriptan- oral and one injectable formulation when multi-source generics are available	▪ Eletriptan (Relpax) ▪ Zolmitriptan (Zomig) ▪ Sumatriptan/naproxen (Treximet)	▪ **Sumatriptan needle-free injection (Sumavel DosePro** ▪ Almotriptan (Axert) ▪ Frovatriptan (Frova) ▪ Naratriptan (Amerge)	Sumavel DosePro: Pending 60 days	-	August 2008	-

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Feb 2010	Narcotic Analgesics	New Drug Fentanyl Citrate Buccal Soluble Film (Onsolis)	• morphine sulfate IR 15, 30 mg • morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg • oxycodone/APAP 5/325 mg • hydrocodone/APAP 5/500 mg • codeine/APAP 30/300 mg • codeine/APAP elixir 12/120 mg/5 mL • tramadol IR	• **Fentanyl buccal soluble film (Onsolis)** • Fentanyl transdermal system (Duragesic, generics); transmucosal tablet (Fentora); & transmucosal lozenge (Actiq; generics) • Codeine • Hydromorphone (Dilaudid) • Levorphanol • Meperidine • Methadone • Morphine products (other than BCF selections), Kadian and Avinza (ER products) • Morphine sulfate ER / naltrexone (Embeda) Feb 2010 • Opium tincture • Opium/belladonna alkaloids(suppositories) • Oxycodone IR • Oxycodone ER(Oxycontin) • Oxymorphone (Opana) • Oxycodone/ASA • Oxycodone/APAP other than BCF selections • Buprenorphine injection • Butorphanol • Pentazocine/naloxone • Propoxyphene • Nalbuphine • Codeine / APAP (other than BCF selections) • Codeine / ASA • Codeine / ASA / carisoprodol • Codeine / caffeine / butalbital / APAP or ASA • Dihydrocodeine / caffeine / APAP or ASA • Hydrocodone / APAP • Pentazocine / APAP • propoxyphene / APAP • Propoxyphene / ASA / caffeine • Tramadol / APAP • Codeine	• Tramadol ER (Ultram ER) Feb 07 • Tramadol ER (Ryzolt) Nov 09 • Tapendatol (Nucynta) Nov 09	Not applicable	-	Feb 2010 Feb 2007 Nov 2009	• Fentanyl Buccal Soluble Film (Onsolis) to remain UF

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	**UF Medications** **MTFs may have on formulary (continued)**	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Feb 2010 (cont)				• **Fentanyl transdermal system** • **Fentanyl transmucosal tablet** • **Fentanyl transmucosal lozenge** • **Fentanyl buccal soluble film** • **Hydromorphone** • **Levorphanol** • **Meperidine** • **Methadone** • **Morphine sulfate ER 24hr** • **Morphine sulfate / naltrexone hydrochloride ER** • **Opium tincture** • **Opium / belladonna alkaloids (suppositories)** • **Oxycodone ER** • **Oxycodone IR** • **Oxymorphone** • **Oxycodone / ASA** • **Oxycodone / APAP** • **Buprenorphine injection** • **Butorphanol** • **Pentazocine / naloxone** • **Propoxyphene** • **Nalbuphine** • **Codeine / APAP** • **Codeine / ASA** • **Codeine / ASA / Carisoprodol** • **Codeine / caffeine / butalbital / APAP or ASA** • **Dihydrocodeine / Caffeine / ASA or APAP** • **Hydrocodone / APAP** • **Pentazocine / APAP** • **Propoxyphene / APAP** • **Propoxyphene / ASA / caffeine** **Tramadol / APAP**				

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
May 2010	Nasal Allergy Drugs	BCF Removal Fluticasone propionate nasal spray (Flonase; generics)	▪ Azelastine (Astelin)	▪ **Fluticasone propionate (generic Flonase)** ▪ **Flunisolide (Nasalide, generics)** ▪ **Ipratropium (Atrovent, generics)** ▪ **Mometasone (Nasonex)**	▪ Azelastine with sucralose (Astepro) ▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ	Pending Upon signing of minutes	-	Nov 05 & Aug 07 for Veramyst) Nov 08 May 08 (Astepro)	-
May 2010	Non-Basal Insulins	BCF Addition	▪ Novolog pens and cartridges ▪ Novolog Mix pens and cartridges	▪ **Not applicable**	▪ Not applicable	Pending upon signing of minutes	-	-	-Joint National Contract with the DoD/VA -Novolog & Novolog Mix vials remain BCF

* New Drug—refers to a new FDA-approved drug in a class previously reviewed for Uniform Formulary (UF) status

APAP: acetaminophen

BPH: benign prostatic hyperplasia

ER: extended release

IR: immediate release

Appendix E—Table of Abbreviations

BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPH	Benign prostatic hyperplasia
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CMA	cost minimization analysis
CRP	C-reactive protein
CV	cardiovascular
DM	diabetes mellitus
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HDL	high density lipoprotein cholesterol
HUS-TTP	hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura
IR	immediate release
LDL	low density lipoprotein cholesterol
LIP-1	Antilipidemic-1s drug class
MARR	Mandatory Agreement for Retail Refunds
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
POS	point of service
PPI	Proton pump inhibitor drug class
QL	quantity limit
REMS	Risk evaluation and mitigation strategy
SED-1	Sedative hypnotic-1 drug class
TG	Triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPHARM	TRICARE Pharmacy Benefit Program
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
February 2010

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on February 17, 2010, and February 18, 2010, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of February minutes**—Allen W. Middleton, Acting Director, approved the minutes of the November 2009 DoD P&T Committee meeting on February 3, 2010.

2. **Corrections to August minutes**—The P&T Committee clarified that the Prior Authorization (PA) for Phosphodiesterase-5 (PDE-5) inhibitors for erectile dysfunction is not subject to a one-year expiration. Minutes from the May 2005 and August 2009 P&T Committee meetings revealed a discrepancy that required corrective action.

   a) ***COMMITTEE ACTION***—The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) that the PA for the PDE-5 inhibitors is not subject to the one-year expiration.

   Acting Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Narcotic Analgesics—Morphine sulfate extended release (ER)/naltrexone capsules (Embeda)

Relative Clinical Effectiveness—Embeda is the first abuse-deterrent formulation of morphine to reach the market. Each capsule contains round pellets of morphine sulfate ER that surround a naltrexone core. Morphine sulfate ER/naltrexone is a Schedule II controlled substance and is classified as a high-potency single analgesic agent in the narcotic analgesic drug class, which was last reviewed in February 2007. Embeda is

indicated for the treatment of moderate to severe pain in adults when continuous, around-the-clock analgesia is required for an extended period of time.

Morphine is a pure opioid agonist selective for the mu receptor, while naltrexone is a mu antagonist that reverses the effects of the mu agonists. When the capsules are taken whole as directed, the morphine provides analgesia with no clinical effects from the naltrexone. Attempts to tamper with the pellets either by crushing or dissolving will cause a rapid release and absorption of the naltrexone, antagonizing the effects of the morphine released.

The unpublished trial used to gain FDA approval reported that Embeda was superior to placebo in relieving pain in patients with osteoarthritis. A study in recreational opioid users reported reduced drug liking for crushed Embeda capsules and whole Embeda capsules, when compared to immediate release morphine solution. The clinical significance of reduction in drug liking is unknown. The product labeling states, "There is no evidence that the naltrexone in Embeda reduces the abuse liability of Embeda." There are no other abuse deterrent opioids on the market, though several are currently in development.

The safety profile for Embeda reflects that of other morphine sulfate ER products and narcotic analgesics on the Uniform Formulary (UF). Crushing, chewing or dissolving pellets can cause fatal release of morphine or precipitate withdrawal in opioid-tolerant individuals.

The clinical evaluation for Embeda included, but was not limited to, requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) there was a potential benefit, though not yet proven, that morphine sulfate ER/naltrexone (Embeda) has a blunted drug-liking response, compared to other UF high-potency narcotic analgesics.

Relative Cost-Effectiveness—The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the other currently available narcotic analgesics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of the agent. Results from the CMA showed the projected weighted average cost per day for Embeda is higher than the other formulary narcotic analgesics, including transdermal fentanyl, morphine sulfate ER (Avinza and MS Contin), oxycodone (OxyContin), and oxymorphone (Opana ER). However, the projected weighted average cost per day for Embeda was lower than the UF agent morphine sulfate (Kadian).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) morphine sulfate ER/naltrexone (Embeda) was cost effective relative to the other UF agents in the narcotic analgesics drug class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 3 opposed, 1 abstained, 0 absent) morphine sulfate ER/naltrexone capsules (Embeda) be designated formulary on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION***—The P&T Committee considered the BCF status of morphine sulfate ER/naltrexone (Embeda). Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) morphine sulfate ER/naltrexone (Embeda) would not be added to the BCF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

B. Attention Deficit/Hyperactivity Disorder (ADHD)—Guanfacine extended release (ER) tablets (Intuniv)

Relative Clinical Effectiveness—Intuniv is indicated for the treatment of ADHD in children and adolescents aged 6 to 17 years. Intuniv is included in the ADHD/Narcolepsy drug class, which was reviewed in November 2006.

Guanfacine immediate release (IR) (Tenex, generics) is FDA-approved for treating hypertension, but is well accepted for off-label use in ADHD. Intuniv is dosed once daily for ADHD and is approved as monotherapy. Guanfacine IR is usually dosed twice daily for ADHD. Guanfacine is an alpha-2A agonist and is not a scheduled substance, unlike the stimulants (methylphenidate and amphetamine). Clonidine is another alpha-2A agonist used off-label for ADHD. Clonidine is available in tablets and transdermal formulations. Intuniv has a longer half-life than clonidine and causes less sedative and hypotensive effects.

Atomoxetine (Strattera), another nonstimulant, is FDA-approved as monotherapy for children with ADHD and has a different mechanism of action (norepinephrine reuptake inhibitor) than guanfacine. Strattera has more established efficacy data than Intuniv, but safety concerns include suicidal ideation and hepatotoxicity.

There are no direct comparative trials with Intuniv and other ADHD nonstimulants (guanfacine IR or Strattera). In two 8-week studies, Intuniv was superior to placebo in reducing symptoms associated with ADHD. Its efficacy in adolescents and the optimal dose for heavier adolescents remain to be determined. The duration of action of Intuniv ranged between 8 to 12 hours and was dose-dependent. Longer-term trials are necessary to delineate its place in therapy.

The clinical evaluation for Intuniv included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that guanfacine ER (Intuniv) has a different mechanism of action and adverse effect profile than Strattera. The P&T Committee acknowledged that Intuniv offers the convenience of once-daily dosing and a defined dosing regimen compared to guanfacine IR and clonidine, but there is insufficient data to suggest whether there are additional clinical advantages compared to the other UF nonstimulants.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of guanfacine ER (Intuniv) in relation to the efficacy, safety, tolerability, and clinical outcomes of the ADHD agents in the ADHD/Narcolepsy UF drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Intuniv relative to other UF ADHD agents. Results from the CMA showed the projected weighted average cost per day for Intuniv is higher than other formulary ADHD agents except the clonidine transdermal formulation.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) that guanfacine ER (Intuniv) is comparable in cost to branded stimulant and nonstimulant products in the ADHD/Narcolepsy drug class. In comparison to generics in this class, the P&T Committee determined that the higher daily cost for Intuniv was offset by its FDA-approved dosing regimen and once-daily administration.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (11 for, 3 opposed, 1 abstained, 1 absent) guanfacine ER tablets (Intuniv) be designated formulary on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee considered the BCF status of guanfacine ER (Intuniv). Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) guanfacine ER (Intuniv) would not be added to the BCF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

C. Newer Sedative Hypnotics—Zolpidem sublingual tablets (Edluar)

Relative Clinical Effectiveness—Zolpidem sublingual (SL) tablets (Edluar) is a newer sedative hypnotic approved for the short-term treatment of insomnia characterized by difficulties in sleep initiation. The newer sedative hypnotics were last reviewed in February 2007. Generic zolpidem immediate release (IR) oral tablets are currently included on the BCF.

Edluar was approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act by demonstrating bioequivalence to zolpidem IR (Ambien) tablets. The SL tablets disintegrate when placed under the tongue and are not swallowed. The pharmacokinetic profiles of Edluar, Ambien, and zolpidem extended release (Ambien CR) tablets are similar with regard to bioavailability, time to reach maximal concentration, half-life, protein binding, and elimination. There are no direct comparative trials evaluating the final commercially-marketed formulation of Edluar

with zolpidem IR tablets or other newer sedative hypnotics. Two small studies comparing an early zolpidem SL formulation with Ambien reported sleep onset measures were 6 to 7 minutes faster with the SL product than Ambien; however, the clinical relevance of this difference is unknown The safety profile for Edluar reflects that of other zolpidem formulations (e.g., Ambien and Ambien CR).

The clinical evaluation for Edluar included, but was not limited to, the requirements stated in 32 CFR 199.21(3)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (16 for, 0 against, 0 abstained, 0 absent) that although zolpidem SL tablets (Edluar) offer an alternative sedative hypnotic formulation for patients with swallowing difficulties, there is insufficient data to conclude it offers improved efficacy, safety, or tolerability in the treatment of insomnia compared to zolpidem IR tablets.

Relative Cost-Effectiveness—The P&T Committee evaluated the costs of zolpidem SL tablets (Edluar) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other newer sedative hypnotics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Edluar tablets. Results from the CMA showed the projected weighted average cost per day for Edluar is higher than the UF newer sedative hypnotic zolpidem IR and nonformulary (NF) newer sedative hypnotics, ramelteon (Rozerem) and zaleplon (Sonata).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) zolpidem SL (Edluar) was not cost effective relative to the other UF and NF agents in the newer sedative hypnotics drug class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 0 absent) that zolpidem SL tablets (Edluar) be designated NF on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA***—Based on the clinical evaluation of zolpidem SL tablets (Edluar) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Edluar. (See Appendix B for full MN criteria).

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

D. Renin Angiotensin Antihypertensive Agents (RAAs)—Telmisartan/ amlodipine tablets (Twynsta)

Relative Clinical Effectiveness—Twynsta is a fixed-dose combination product containing telmisartan (Micardis) and amlodipine (Norvasc, generics). It is the third two-drug combination product containing an angiotensin receptor blocker (ARB; Micardis) and dihydropyridine calcium channel blocker (DHP CCB; amlodipine) to reach the market. Azor (olmesartan [Benicar]/amlodipine) and Exforge (valsartan [Diovan]/amlodipine) were the first entrants on the market. Twynsta is solely indicated for treating hypertension; it can be substituted for the individual titrated components or used as initial therapy in patients likely to require two or more drugs to control blood pressure (BP). Current national guidelines for treating hypertension recommend when more than one drug is needed for BP control, one of the components should comprise a diuretic.

Telmisartan is currently designated as formulary on the UF; amlodipine is designated as BCF. Twynsta is included in the RAAs drug class, which is comprised of several

subclasses (ARBs, angiotensin-converting enzyme (ACE) inhibitors, direct renin inhibitors and their combinations with CCBs or diuretics). The RAAs class will be re-evaluated at an upcoming meeting.

Treatment with various combinations of telmisartan/amlodipine was shown in one randomized trial to significantly reduce BP compared to baseline and placebo. There are no trials evaluating clinical outcomes of mortality or morbidity with Twynsta, although outcomes trials are available with the individual components.

The adverse reaction profile for Twynsta reflects that of the individual components. Although no studies are available specifically addressing the potential for increased compliance with Twynsta over the individual components administered together, other studies have shown an increase in persistence with fixed-dose antihypertensive combination products.

The clinical evaluation for Twynsta included, but was not limited to the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) telmisartan/amlodipine (Twynsta) did not have a significant, clinically meaningful, therapeutic advantage in terms of safety, effectiveness, or clinical outcome over other antihypertensive drugs included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the combination antihypertensive agents in this class as well as the individual components, telmisartan and amlodipine. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Twynsta relative to other UF agents in this class. Results from the CMA showed the projected weighted average cost per day for Twynsta is higher than the other formulary combination antihypertensive agents, including triple-therapy oral agent amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) and the individual components amlodipine and telmisartan (Micardis).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 0 abstained, 0 absent) telmisartan/amlodipine (Twynsta) is not cost effective relative to the other combination antihypertensive agents in this class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15

for, 0 opposed, 1 abstained, 0 absent) telmisartan/amlodipine (Twynsta) be designated NF on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation for telmisartan/amlodipine (Twynsta) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Twynsta. (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. RAAs—Aliskiren/valsartan tablets (Valturna)

Relative Clinical Effectiveness—Valturna is a fixed-dose combination product containing the ARB valsartan (Diovan) and aliskiren (Tekturna), a direct renin inhibitor. Tekturna is also available in a fixed-dose combination tablet containing the diuretic hydrochlorothiazide (HCTZ); both Tekturna and Tekturna HCT are designated as formulary on the UF. Valsartan (Diovan) is designated NF. Valturna is included in the RAAs drug class, which will be re-evaluated at an upcoming meeting.

Valturna is indicated for treating hypertension. It has other indications based on clinical trials showing positive clinical outcomes; outcomes trials with Tekturna are currently underway. Current national guidelines for treating hypertension have not yet addressed the place in therapy for direct renin inhibitors, although updated guidelines are anticipated later this year.

Treatment with Valturna was shown in one randomized trial to significantly reduce BP compared to placebo or administering the components individually. However, the BP reduction seen with Valturna in this study was not as large as that seen in other studies evaluating fixed-dose antihypertensive combination products. The adverse reaction profile for Valturna reflects that of the individual components.

The clinical evaluation for Valturna included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that although aliskiren/valsartan (Valturna) has a unique mechanism of action due to the direct renin inhibitor component and offers the potential for increased persistence, it did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive drugs included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the combination antihypertensive agents in this class as well as the individual components, aliskiren and valsartan. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of Valturna compared to other UF agents. Results from the CMA showed the projected weighted average cost per day for Valturna is higher than the other formulary combination antihypertensive agents, including triple-therapy oral agent Exforge HCT and the individual components, Tekturna and Diovan.

Relative Cost-Effectiveness Conclusion—The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) that aliskiren/valsartan (Valturna) is not cost effective relative to the other combination antihypertensive agents in this class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 0 opposed, 2 abstained, 0 absent) aliskiren/valsartan (Valturna) be designated NF on the UF.

   Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of aliskiren/valsartan (Valturna) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Valturna. (See Appendix B for full MN criteria).

   Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

   Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

IV. UF DRUG CLASS REVIEWS

A. Basal Insulins

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the long-acting basal insulin analogues (e.g., basal insulins) for the treatment of diabetes mellitus (DM). Insulin detemir (Levemir) and insulin glargine (Lantus) were FDA approved on June 16, 2005, and April 30, 2000, respectively. Lantus and Levemir are available in both vials and prefilled pen devices (Lantus SoloStar and Levemir FlexPen). Lantus vials are currently on the BCF. Information regarding the safety, effectiveness, and clinical outcomes of the long-acting basal insulin analogues was considered. Neutral Protamine Hagedon (NPH) is an intermediate-acting basal insulin. NPH is not classified in the long-acting basal insulins UF drug class; it remains a BCF drug. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

MHS expenditures for the long-acting basal insulin analogues exceeded $4M per month at the retail, mail order, and MTF points of service (POS) from January 2008 to December 2009. In the MHS, Lantus is the highest utilized basal insulin. Lantus vials were dispensed three times more frequently than the next highest utilized drug, Lantus SoloStar, followed by Levemir FlexPen.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding the basal insulin drug class:

1. With regard to efficacy, the following conclusions were made:
   a) In pivotal trials, both Levemir and Lantus produced similar reductions in glycosylated hemoglobin A1c (HbA1c), when compared to NPH insulin in subjects with type-1 or type-2 DM.

      In head-to-head studies, there was no clinically relevant difference in the reduction in HbA1c between Levemir and Lantus in subjects with type-1 or type-2 DM. The absolute HbA1c difference was <0.4% between the two drugs.

   b) In head-to-head studies, there was a statistically significant difference in the reduction in fasting plasma glucose (FPG) values between Levemir and Lantus in subjects with type-1 DM; larger FPG reductions were seen with Lantus. This difference was not observed in subjects with type-2 DM. The clinical significance of this finding is unknown.

   c) In head-to-head studies, the total Levemir dose required to achieve goal HbA1C levels (<7%) was larger than the dose of Lantus used to achieve goal HbA1C levels in subjects with type-1 DM. Levemir was dosed twice-daily more often

2. With regard to safety and tolerability, the following conclusions were made:
   a) Existing evidence does not support clinically relevant differences concerning hypoglycemia or weight gain between Levemir and Lantus. In subjects with type-2 DM, the difference in weight gain between Levemir (daily and twice daily dosing) vs. Lantus (once daily dosing) was 0.9 kg ($p=0.01$). Once daily dosing of Levemir caused less weight gain than twice daily dosing (absolute difference 1.4 kg; $p<0.001$). Once daily dosing of Levemir caused less weight gain than once daily dosing of Lantus (absolute difference 1.6 kg; $p<0.001$). The difference in weight gain was similar when twice daily dosing of Levemir was compared to once daily dosing of Lantus (absolute difference 0.2 kg).
   b) There is insufficient evidence to determine if there are clinically relevant differences between Levemir and Lantus with respect to cancer risk. Observational studies raised concerns of an association between the use of Lantus and cancer incidence. These studies had inconsistent findings and many study design flaws. FDA is uncertain of this association.
3. With regard to other factors
   a) There are no clinically relevant differences between the pen devices for Lantus SoloStar and Levemir FlexPen in terms of refrigeration requirements and expiration date after opening, with the exception that Levemir is stable for 42 days and Lantus is stable for 28 days.
   b) Patient preference studies report that patients overall prefer using insulin pen devices compared to insulin vials. Most studies have shown no patient preferences among various pen devices.
   c) A request for input from MTF providers revealed that the majority of responders ranked Lantus as their first preference for a basal insulin, followed by Levemir as the second choice, primarily due to perceived differences in efficacy and availability on the local formulary. The majority of responders stated that availability of one basal insulin on the local formulary was adequate to meet their prescribing needs.

Relative Cost-Effectiveness—In considering the relative cost-effectiveness of the basal insulins, the P&T Committee evaluated the costs in relation to the efficacy, safety, tolerability, and clinical outcomes. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA and budget impact analysis (BIA) were used to evaluate the cost-effectiveness of the basal insulins.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

a) CMA results of the basal insulins revealed that Lantus vials were more cost effective than Levemir vials based on cost per ml of treatment. CMA results of the basal insulins revealed that Lantus SoloStar pen devices were more cost effective than Levemir FlexPen pen devices based on cost per ml of treatment. Cost per ml of treatment was calculated using average quarterly consumption rates for Lantus vials and Lantus SoloStar pen devices and Levemir vials and Levemir FlexPen pen devices.

b) The potential impact of scenarios with selected basal insulins designated formulary or NF on the UF was evaluated using BIA. Scenarios evaluating the impact of designating basal insulins on the BCF were also considered. Results from the BIA for the basal insulins revealed that placing Lantus vials and Lantus SoloStar pen devices on the BCF and UF, with Levemir vials on the UF, and designating Levemir FlexPen pen devices NF was the most cost-effective scenario overall.

c) BIA results showed that Levemir vials and Levemir FlexPen pen devices were more costly than Lantus vials and Lantus SoloStar pen devices in all scenarios that do not require automated prior authorization. Lantus vials and Lantus SoloStar pen devices were more costly than Levemir vials and Levemir FlexPen pen devices in one scenario involving an automated prior authorization. However, The P&T Committee decided that an automated prior authorization was not clinically appropriate for the basal insulin class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) to recommend the following:

    a) Insulin glargine vials (Lantus), insulin glargine pen devices (Lantus SoloStar) and insulin detemir vials (Levemir) remain classified as formulary on the UF.

    b) Insulin detemir pen devices (Levemir FlexPen) be designated NF on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of insulin detemir pen devices (Levemir FlexPen) and the conditions for establishing MN for a NF medication, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Levemir FlexPen. (See Appendix B for full MN criteria).

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

4. ***COMMITTEE ACTION: BCF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) that insulin glargine vials (Lantus) remain BCF, and insulin glargine pen devices (Lantus SoloStar) be added to the BCF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Antihemophilic Agents—Plasma-derived/Recombinant Factor VIII and Factor IX products

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the antihemophilic agents. The class was divided into the factor VIII and factor IX concentrates; and the factor VIII/von Willebrand (vWF) factor complexes; human prothrombin concentrate complexes (PCCs); and inhibitor bypassing products. The antihemophilic agents have not previously been reviewed for UF placement; they are an extended core formulary (ECF) drug class.

Purified factor VIII drugs are used to treat hemophilia A and are manufactured from two sources: plasma-derived (human) and recombinant. The human factor VIII products include Hemofil M, Koate-DVI, and Monoclate-P. The recombinant factor VIII products include Advate, Helixate FS, Kogenate FS, Recombinate, Refacto, and Xyntha. Although Refacto is still available for use, it was no longer manufactured at the time of this review and, therefore, not considered for ECF status.

Purified factor IX drugs used to treat hemophilia B are likewise derived from two sources: human and recombinant. The human factor IX concentrates include AlphaNine SD and MonoNine. There is only one recombinant factor IX product: BeneFIX. Information was considered regarding the safety, effectiveness, and clinical outcomes of the factor VIII and factor IX subclasses of the antihemophilic agents. Only uses that pertain to the outpatient pharmacy benefit were considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Military Health System (MHS) expenditures for the all antihemophilic agents (factor VIII, factor IX, factor VIII/vWF complexes, PCCs, and inhibitor bypassing products) exceeded $39M from December 2008 to November 2009 predominantly at the retail POS. There are approximately 190 unique utilizers in the MHS. There were no MHS utilizers of Monoclate-P or AlphaNine SD during this time period.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding purified factor VIII and IX concentrates:

1. With regard to efficacy, the following conclusions were made:

a) There are no head-to-head comparative trials evaluating the factor VIII or factor IX products. Efficacy studies were limited to open-label clinical trials with no active comparators.

b) Many products obtained FDA approval based on pharmacokinetic demonstration of bioequivalence to previously approved (e.g., earlier generation) products following improvements in production and viral depletion or inactivation methods.

c) There is no evidence to conclude that there are clinically relevant differences in efficacy between the respective factor VIII and factor IX concentrates.

2. With regard to safety and tolerability, the P&T Committee agreed that, although the overall risk is small, there is a lower risk of viral transmission with recombinant products than with plasma-derived products. There is insufficient evidence to conclude there are clinically relevant differences in safety between the recombinant factor VIII products.

3. With regard to other factors, the following conclusions were made:

   a) National professional group guidelines and national hemophilia patient advocacy groups caution against switching between products once a patient is stabilized, due to potentially detrimental outcomes, including development of immunogenicity.

   b) There are differences among the factor VIII and factor IX products with regard to viral deactivation/depletion methods, storage and refrigeration requirements, vial sizes available, reconstitution and administration kits, patient support programs, and stabilizers/cell culture media used in recombinant products.

Relative Cost-Effectiveness—In considering the relative cost-effectiveness of pharmaceutical agents in the antihemophilic plasma-derived/recombinant factor VIII and factor IX subclass, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMAs were used to evaluate the cost-effectiveness of the plasma-derived/recombinant factor VIII and factor IX subclass.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

a) CMA results for the antihemophilic factor VIII agents revealed that Xyntha was the most cost-effective recombinant factor VIII product based on cost per unit of treatment. Cost per unit of treatment was calculated using the

b) CMA results for the antihemophilic factor IX agents revealed that BeneFIX was the most cost-effective antihemophilic recombinant factor IX product based on the cost per unit of treatment. Cost per unit of treatment was calculated using average drug price per unit rates for the recombinant factor IX products AlphaNine SD and MonoNine.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (11 for, 1 opposed, 3 abstained, 1 absent):

   a) All factor VIII and factor IX products recommended for inclusion on the UF had existing Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP) or a required Mandatory Agreement for Retail Refunds (MARR). No products recommended for NF designation on the UF have required pricing agreements.

   b) The factor VIII products Koate-DVI, Kogenate FS, Refacto, and Xyntha, and the factor IX products AlphaNine SD and BeneFIX remain classified as formulary on the UF.

   c) The factor VIII products Advate, Hemofil M, Helixate FS, Monoclate-P, and Recombinate, and the factor IX product MonoNine be designated NF on the UF.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of the plasma-derived and recombinant factor VIII and factor IX products and the conditions for establishing MN for a NF medication, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1

absent) MN criteria for Advate, Hemofil M, Helixate FS, Monoclate-P, Recombinate, and MonoNine. (See Appendix B for full MN criteria.)

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 180-day implementation period in the retail network and mail order, and at MTFs no later than a 180-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

4. ***COMMITTEE ACTION: ECF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent):

   a) The factor VIII product Xyntha be designated as ECF on the UF.

   b) The factor IX product BeneFIX be designated as ECF on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. Antihemophilic Agents—Human Factor VIII/vWF, PCCs, and Inhibitor Bypassing products (Recombinant VIIa Factor and Human Activated PCC) Products

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the remainder of the antihemophilic drug class, comprised of the human factor VIII/vWF complexes, the human PCCs, and the inhibitor bypassing products.

Humate-P and Alphanate are the two human factor VIII products containing a measured amount of vWF that are used to treat certain types of von Willebrand disease and to replace factor VIII in patients with hemophilia A. Human PCCs were formerly the treatment of choice for hemophilia B before highly purified products became available and now are used to treat factor II and factor X deficiency. The PCCs include Bebulin VH and Profilnine SD. The inhibitor bypassing products include one recombinant activated factor VII, NovoSeven RT, and one human activated PCC, Feiba VH. These two products are indicated for use in patients with hemophilia A or hemophilia B who have developed inhibitors, and are used to treat bleeding episodes, or to prevent bleeding episodes during surgical interventions.

Information was considered regarding the safety, effectiveness, and clinical outcomes of the factor VIII/vWF complexes, the PCCs, and the inhibitor bypassing subclass of the antihemophilic agents. Only uses that pertain to the outpatient drug benefit were considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1). There were no MHS utilizers of Humate-P or Profilnine SD from December 2008 to November 2009.

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 2 absent) the following clinical effectiveness conclusions:

1. With regard to efficacy, the following conclusions were made:
    a) There is no evidence to conclude that there are clinically relevant differences in efficacy between NovoSeven RT and Feiba VH in the outpatient treatment of bleeding episodes in hemophilia patients who have inhibitors.

b) There is no evidence to conclude that there are clinically relevant differences in efficacy between Bebulin VH and Profilnine SD in the outpatient treatment of factor II or factor X deficiency.

c) There is no evidence to conclude that there are clinically relevant differences in efficacy between Humate-P and Alphanate in the outpatient treatment of von Willebrand disease or hemophilia A.

2. With regard to safety and tolerability, the P&T Committee agreed that:

a) Although the risk is small, there is a lower risk of viral transmission with a recombinant product (NovoSeven RT) than with a plasma-derived product (Feiba VH). Feiba VH may also cause an anamnestic response in patients with inhibitors who are classified as high responders to therapy, and can cause anaphylaxis or nephrotic syndrome in hemophilia B patients who have developed inhibitors. Both products carry a very low risk of thrombotic complications. Feiba VH has a warning advising extreme caution when using in patients with hepatic impairment.

b) Bebulin VH contains heparin and may not be appropriate to use in patients with a history of type II heparin induced thrombocytopenia (HIT); otherwise, there is no evidence that there are clinically relevant differences in safety between Bebulin VH and Profilnine SD.

c) Alphanate contains heparin and may not be appropriate to use in patients with a history of type II HIT; otherwise, there is no evidence that there are clinically relevant differences in safety between Humate-P and Alphanate.

3. With regard to other factors:

a) Feiba VH has a longer half-life than Novoseven RT and may be more appropriate when considering prophylactic treatment in a hemophilia patient who has developed inhibitors and is classified as a high responder to therapy.

c) National professional group guidelines and national hemophilia patient advocacy groups caution against switching between products once a patient is stabilized, due to potentially detrimental outcomes, including development of immunogenicity.

There are differences among the factor VIII/vWF concentrates, the human PCCs, and the inhibitor bypassing products with regard to viral deactivation/depletion methods, storage and refrigeration requirements, vial sizes available, reconstitution and administration kits, and patient support programs.

Relative Cost-Effectiveness—In considering the relative cost-effectiveness of pharmaceutical agents in the human factor VIII/vWF, PCCs, and inhibitor bypassing products subclass, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMAs were used to evaluate the cost-effectiveness of the human factor VIII/vWF, PCCs, and inhibitor bypassing products subclass.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (13 for, 0 opposed, 2 abstained, 1 absent) the following:

a) CMA results for the Factor VIII/vWF subgroup revealed that Alphanate was the most cost-effective agent based on cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for Alphanate and Humate-P.

b) CMA results for the PCCs subgroup revealed that Profilnine SD was the most cost-effective agent based on cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for Bebulin VH and Profilnine SD.

c) CMA results for the inhibitor bypassing products subgroup revealed that NovoSeven RT was the most cost-effective agent based on a cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for NovoSeven RT and Feiba VH.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 1 absent):

    a) All factor VIII and factor IX products recommended for inclusion on the UF had existing UF VARR submissions at or below the FCP or a required MARR. No products recommended for NF designation on the UF have required pricing agreements.

    b) The factor VIII/vWF product Alphanate, the human PCC product Profilinine SD, and the inhibitor bypassing product NovoSeven RT remain classified as formulary on the UF.

c) The factor VIII/vWF product Humate-P, the human PCC product Bebulin VH, and the inhibitor bypassing product Feiba VH be designated NF on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of the factor VIII/vWF complexes, the human PCCs, and the inhibitor bypassing products subclass of the antihemophilic agents, and the conditions for establishing MN for a NF medication, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for Humate-P, Bebulin VH, and Feiba. (See Appendix B for full MN criteria).

   Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 180-day implementation period in the retail network and mail order, and at MTFs no later than a 180-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval of the DoD P&T Committee minutes.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

V. UTILIZATION MANAGEMENT—PA/QUANTITY LIMITS (QL)

A. PDE-5 Inhibitors—PA post-prostatectomy: At the August 2009 P&T Committee meeting, PA criteria for the PDE-5 inhibitors were expanded to include restoration/preservation of erectile function following prostatectomy. Clarification regarding the length of therapy and other issues was requested in order to fully operationalize this criterion at the retail network and mail order pharmacy. The P&T Committee reviewed the clinical evidence regarding the use of PDE-5 inhibitors following prostatectomy, including duration of therapy, and also reviewed the requirements from other civilian health plans.

1. ***COMMITTEE ACTION: PA***—The P&T Committee voted (13 for, 0 opposed, 1 abstained, 2 absent) to recommend limiting the length of therapy to one year for the PDE-5s when used following prostatectomy.

   Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

B. Sumatriptan needle-free injection (Sumavel DosePro)—QL: A new needle-free sumatriptan injection (Sumavel DosePro) has been marketed. Sumavel DosePro will be reviewed as a new FDA-approved drug in the triptan drug class at an upcoming DoD P&T Committee meeting. QLs are currently in place for both oral and other injectable formulations of sumatriptan (Imitrex, generics) and the other oral triptans, which are consistent with the product labeling.

1. ***COMMITTEE ACTION: QL***—The P&T Committee voted (13 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs of 9 mL (18 units)/90 days in the mail order pharmacy and 3 mL (6 units)/30 days in the retail network, which is

consistent with the recommended dosing from the product labeling and avoids breaking apart packages.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. ITEMS FOR INFORMATION

A. **Pharmacy Outcomes Research Team (PORT)**—The PORT briefed the P&T Committee on study results concerning the automated PA program for the proton pump inhibitors.

B. **Department of Veterans Affairs (VA)/DoD Joint Contracting Initiatives**

BCF/ECF Issues—The P&T Committee was briefed regarding the VA National Acquisition Center contract for insulin needles. In March 2009, the VA/DoD joint national contract for insulin needles was changed to include the 30 ½" and 31 5/16" gauge/length needle sizes with 0.3, 0.5, and 1 ml volumes. The current DoD BCF insulin needles are 28 ½" gauge/length needles with 0.5 and 1ml volumes. DoD anticipates increased availability of the 31 5/16" gauge/length needle. Historical utilization from DoD prime vendor data shows a significant usage of the 0.3 ml volume syringes.

1. ***COMMITTEE ACTION: UF RECOMMENDATION***—Based on the results of the information presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) to recommend: 1) 31 5/16" gauge/length needle sizes with the 0.3, 0.5, and 1 ml volumes be added to the BCF; 2) 28 ½" gauge/length needles with 0.5 and 1 ml volumes be deleted from the BCF; and 3) 30 ½" gauge/length needles with 0.5 and 1 ml volumes will be maintained as formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. **Exenatide injection (Byetta)—PA:** Due to a new FDA indication for Byetta for use as monotherapy in patients with type-2 DM, the P&T Committee received a request to re-

criteria were established by the P&T Committee in August 2006, based on Byetta's potential use for indications not covered by TRICARE (i.e., weight loss) and/or not supported by clinical evidence. Since the original establishment of the PA, there have been updates to the product labeling due to safety concerns, including pancreatitis. The injectable drugs for DM, including Byetta and a similar product recently approved by the FDA, liraglutide injection (Victoza), will be reviewed at an upcoming meeting. The P&T Committee agreed to defer action until the class is reviewed.

VII. NATIONAL DEFENSE AUTHORIZATION ACT, SECTION 703—INCLUSION OF TRICARE RETAIL PHARMACY PROGRAM IN FEDERAL PROCUREMENT OF PHARMACEUTICALS UPDATE

The P&T Committee reviewed drugs that were not included on a DoD Retail Refund Pricing Agreement; these drugs are not compliant with Fiscal Year 2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated NF on the UF and will require pre-authorization prior to use in the retail POS and medical necessity in MTFs. These NF drugs will remain available in the mail order POS without pre-authorization. Pre-authorization criteria will be determined at a future DoD P&T Committee meeting. Drugs with and without pricing agreements were systematically classified according to therapeutic and pharmacologic lines. The classification system was based on the American Hospital Formulary System Classification and First Data Bank classification. See Appendix C for the full list of affected medications.

A. ***COMMITTEE ACTION—DRUGS RETAINING UF STATUS***: The P&T Committee recommended by consensus the drugs listed in Appendix C, Section A, retain formulary status on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION—DRUGS RETAINING OR DESIGNATED NF:*** The P&T Committee recommended by consensus the drugs listed in Appendix C, Section B to retain NF status or be designated NF on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION—IMPLEMENTATION DATE FOR PA:*** The P&T Committee recommended by consensus the implementation date will not be prior to July 1, 2010, and not later than 180 days after the minutes of this meeting are signed.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION—TRANSITION DATE AT THE MTF POS:*** The P&T Committee recommended by consensus a transition period at the MTF POS as ending no later than January 1, 2011.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. CLASS OVERVIEWS

Class overviews for the antilipidemic-1s, which includes the statins, niacin and ezetimibe; benign prostatic hyperplasia drugs; the RAAs; and the ophthalmologic-1s class, which includes the ocular antihistamines, mast cell stabilizers and combination antihistamines/mast cell stabilizers, were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed at upcoming meetings.

IX. ADJOURNMENT

The meeting adjourned at 1700 hours on February 17, 2010, and at 1200 hours on February 18, 2009. The next meeting will be in May 2010.

Appendix A—Attendance

Appendix B—Table of Medical Necessity Criteria for Newly Approved Drugs

Appendix C—National Defense Authorization Act, Section 703 Affected Medications

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Appendix E—Table of Abbreviations

SUBMITTED BY:

CDR James Ellzy, MC, USN
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Charles L. Rice, MD

Dr. Charles L. Rice
Acting Director

3 May 2010
(Date)

Appendix A—Attendance

Voting Members Present	
CDR James Ellzy, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center, (Recorder)
Col Everett McAllister, BSC	Deputy Director, Pharmaceutical Operations Directorate
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
CAPT Walter Downs, MC	Navy, Internal Medicine Physician
CAPT David Tanen, MC	Navy, Physician at Large
Col Mike Spilker, BSC	Air Force, Pharmacy Officer
Lt Col Brian Crownover, MC	Air Force, Physician at Large
CDR Phil Blaine *for CAPT Stephanie Simon, MSC*	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician, Alternate
LTC Bruce Lovins, MC	Army, Family Practice Physician, Alternate
COL Ted Cieslak, MC	Army, Physician at Large
COL Peter Bulatao *for COL Carole Labadie, MSC*	Army, Pharmacy Officer, Alternate
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
Mr. David Hurt	Assistant General Counsel, TMA
CDR Francis Williams	Defense Supply Center, Philadelphia
COL Kent Maneval, MS	Defense Medical Standardization Board
Guests	
CDR Rob Hayes	United States Public Health Service/ Indian Health Service
Maj Pete Trang	Lackland AFB
LTC Paula Doulaveris	Army Pharmacovigilence Center
Capt Emily Fusco	Air Force Pharmacy Resident
Dr. Vincent Calabrese	Department of Veteran Affairs

Appendix A—Attendance (continued)

Others Present	
LCDR Joe Lawrence	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
CPT Brian Haney, MC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Libby Hearin	DoD Pharmacoeconomic Center
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Roger Potyk	DoD Pharmacy Outcomes Research Team contractor
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor
Dr. Brian Beck	DoD Pharmacy Operations Center contractor
Ms. Jeanette Cosby	DoD Pharmacy Operations Center contractor

Appendix B—Table of Medical Necessity Criteria for Newly Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Detemir pens (Levemir) **Basal Insulins**	• The patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk (for patients requiring BID dosing with manual dexterity or visual limitations)
Monoclate-P, Hemofil M, Recombinate, Helixate FS, and Advate **Antihemophilic Agents**	• The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk
Humate-P, Bebulin VH, and Feiba VH **Antihemophilic Agents**	• The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk • No alternative formulary agent available (if using Feiba VH for prophylaxis and longer half-life is desired)
Zolpidem sublingual tablets (Edluar) **Newer Sedative Hypnotic Agents**	• No alternative formulary agent available (if patients have swallowing difficulties)
Telmisartan/Amlodipine tablets (Twynsta) **Renin Angiotensin Aldosterone Agents**	• No alternative formulary agent available (if patients have swallowing difficulties)
Aliskiren/Valsartan tablets (Valturna) **Renin Angiotensin Aldosterone Agents**	• No alternative formulary agent available (if patients have swallowing difficulties)

Appendix C—National Defense Authorization Act, Section 703 Affected Medications

A. Drugs Retained as Formulary on the Uniform Formulary

Product Name	Subclass	Manufacturer	Num
TARCEVA	Antineoplastic systemic enzyme inhibitors	GENENTECH, INC.	
TARGRETIN	Oral oncological agents	EISAI INC.	

B. Drugs moved to or retained as nonformulary on the Uniform Formulary

Product Name	Subclass	Manufacturer	Num
FLUOROPLEX	Topical antineoplastic & premalignant lesion medic	ALLERGAN INC.	
PANRETIN	Topical antineoplastic & premalignant lesion medic	EISAI INC.	
SUBOXONE	Narcotic analgesics & combos	RECKITT BENCKIS	
SUBUTEX	Narcotic analgesics & combos	RECKITT BENCKIS	
TAZORAC	Psoriasis medications	ALLERGAN INC.	

Appendix D—Table of Implementation Status of UF Recommendations/Decisions

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Feb 2010	Basal Insulins	UF Review	▪ Insulin glargine (Lantus) vials ▪ Insulin glargine (Lantus Solostar) pens	▪ Insulin levemir (Detemir) vials	▪ Insulin Levemir (Detemir) pens	Pending 60 days			
Feb 2010	Anti-hemophilic Agents	UF Review	▪ Factor VIII: Xyntha ▪ Factor IX: Benefix	▪ Factor VIII: Koate-DVI, Kogenate FS, Refacto, Alphanate ▪ Factor IX: AlphaNine, Profilnine ▪ Inhibitor bypassing product: Novoseven RT	▪ Factor VIII: Advate, Helixate, Hemofil M, Humate-P, Monoclate-P, Recombinate ▪ Factor IX: Mononine; Bebulin VH ▪ Inhibitor bypassing product: Feiba VH	Pending 60 days			
Feb 2010	ADHD Drugs	New Drug Guanfacine ER (Intuniv)	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER ▪ methylphenidate IR	▪ **Guanfacine ER (Intuniv)** ▪ Atomoxetine (Strattera) ▪ Methylphenidate OROS (Concerta ▪ Methylphenidate 30% IR/70% ER (Metadate CD) ▪ Methylphenidate SODAS, SR (Ritalin LA; Ritalin SR) ▪ Mixed Amphetamine salts IR ▪ Dexamphetamine IR ▪ Methamphetamine IR (Desoxyn, generics)	▪ dexmethylphenidate IR, SODAS (Focalin; Focalin SR) ▪ methylphenidate transdermal system (Daytrana) ▪ Lisdexamfetamine (Vyvanse) (Nov 07)	Not applicable		Nov 07 Nov 06	▪ Guanfacine ER (Intuniv) recommended to remain UF (pending)

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Feb 2010	RAAs	New Drug ▪ Telmisartan / amlodipine (Twynsta) ▪ Aliskiren / valsartan (Valturna)	ACE inhibitor ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ▪ ramipril ACE/CCB ▪ amlodipine/benazepril (Lotrel, generics)	ACE Inhibitor ▪ benazepril, HCTZ ▪ enlapril, HCTZ ▪ fosinopril, HCTZ ▪ quinapril, HCTZ ▪ trandolapril (Mavik) ARB ▪ telmisartan, HCTZ (Micardis, Micardis HCT) ▪ losartan, HCTZ (Cozaar, Hyzaar) ▪ candesartan, HCTZ (Atacand, Atacand HCT) ARB/CCB/diuretic ▪ valsartan/ amlodipine/HCTZ (Exforge HCT) Nov 09 DRI ▪ aliskiren, HCTZ (Tekturna; Tekturna HCT)	DRI/CCB ▪ **Aliskiren/valsartan (Valturna)** ARB/CCB ▪ **telmisartan / amlodipine (Tywnsta)** ▪ olmesartan / amlodipine (Azor) ▪ valsartan amlodipine (Exforge) ACE inhibitor ▪ moexipril, HCTZ (Univasc; Uniretic) ▪ perindopril (Aceon) ACE/CCB combos ▪ verapamil / trandolapril (Tarka) ARB ▪ eprosartan, HCTZ (Teveten; Teveten HCT) ▪ irbesartan, HCTZ (Avapro, Avalide) ▪ olmesartan, HCTZ (Benicar; Benicar HCT) ▪ valsartan, HCTZ (Diovan, Diovan HCT)	Pending 60 days		Nov 09 Jun 08 Nov 07 Aug 07 May 07 Feb 06 Aug 05	▪ Telmisartan / amlodipine (Twynsta) and Aliskiren / valsartan (Valturna) recommended for NF (pending)
Feb 2010	Newer Insomnia	New Drug Zolpidem sublingual (Edluar)	▪ Zolpidem IR	▪ Eszopiclone (Lunesta)	▪ Zolpidem CR (Ambien CR) ▪ Zaleplon (Sonata) ▪ Ramelteon (Rozerem) ▪ **Zolpidem sublingual (Edluar)**	Pending 60 days		Feb 07	▪ Zolpidem sublingual (Edluar) recommended for NF (pending) ▪ Step therapy requiring trial of zolpidem IR applies to class

Date	DoD PEC Drug Class	Type of Action*	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Original Review and Updates	Comments
Feb 2010	Narcotic Analgesics	New Drug Morphine sulfate ER / naltrexone (Embeda)	▪ morphine sulfate IR 15, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	▪ **Morphine sulfate ER / naltrexone (Embeda)** ▪ Codeine ▪ Fentanyl transdermal, transmucosal (Actiq), buccal (Fentora) tablets ▪ Hydromorphone (Dilaudid) ▪ Levorphanol ▪ Meperidine ▪ Methadone ▪ Morphine products (other than BCF selections), Kadian and Avinza (ER products) ▪ Opium tincture ▪ Opium/belladonna alkaloids(suppositories) ▪ Oxycodone (Oxycontin) ▪ Oxymorphone (Opana) ▪ Oxycodone/ASA ▪ Oxycodone/APAP other than BCF selections ▪ Buprenorphine injection ▪ Butorphanol ▪ Pentazocine/naloxone ▪ Propoxyphene ▪ Nalbuphine ▪ Codeine / APAP (other than BCF selections) ▪ Codeine / ASA ▪ Codeine / ASA / carisoprodol ▪ Codeine / caffeine / butalbital / APAP or ASA ▪ Dihydrocodeine / caffeine / APAP or ASA ▪ Hydrocodone / APAP ▪ Pentazocine / APAP ▪ propoxyphene / APAP ▪ Propoxyphene / ASA / caffeine ▪ Tramadol / APAP	▪ Tramadol ER (Ultram ER) Feb 07 ▪ Tramadol ER (Ryzolt) Nov 09 ▪ Tapendatol (Nucynta) Nov 09	Not applicable		Feb 07 Nov 09	▪ Morphine sulfate ER / naltrexone (Embeda) to remain UF (pending)

* New Drug—refers to a new FDA-approved drug in a class previously reviewed for Uniform Formulary (UF) status
ACE: angiotensin converting enzyme
ADHD: Attention Deficit / Hyperactivity Disorder drug class
ARB: angiotensin receptor blocker
CCB: calcium channel blocker
DRI: direct rennin inhibitor
HCTZ: hydrochlorothiazide
ER: extended release
IR: immediate release
RAAs: Renin Angiotension Antihypertensive Agents drug class

Appendix E—Table of Abbreviations

ACE	angiotensin converting enzyme
ADHD	attention deficit / hyperactivity disorder drug class
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BP	blood pressure
CCB	calcium channel blocker
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
DHP	dihydropyridine CCB
DM	diabetes mellitus
DoD	Department of Defense
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HbA1c	hemoglobin A1c
HCTZ	hydrochlorothiazide
HIT	heparin-induced thrombocytopenia
IR	immediate release
MARR	Mandatory Agreement for Retail Refunds
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
NPH	neutral protamine hagedon insulin
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PCC	prothromin complex concentrate
PDE-5	phosphodiesterase-type 5 inhibitor drug class
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
POS	point of service
QL	quantity limit
RAAs	renin-angiotensin antihypertensive drug class
SL	sublingual
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPHARM	TRICARE Pharmacy Benefit Program
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds
vWF	von Willebrand factor

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
November 2009

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 5 November 2009 and 6 November 2009 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of August minutes** — Ellen P. Embrey, Acting Director, approved the minutes of the August 2009 DoD P&T Committee meeting on 21 October 2009.

III. REVIEW OF RECENTLY APPROVED FDA AGENTS

A. Multiple Sclerosis - Disease-Modulating Drugs (MS-DMDs) — Interferon Beta-1b Injection (Extavia)

Relative Clinical Effectiveness — Interferon beta-1b injection (Extavia) is an immunomodulator classified as a multiple sclerosis disease-modulating drugs (MS-DMDs). The MS-DMDs were last reviewed for Uniform Formulary (UF) placement in August 2005; no products are currently designated non-formulary.

Extavia is a new branded version of interferon beta-1b, and is the same product as that found under the proprietary name Betaseron. The two manufacturers have agreed to this arrangement. FDA approval for Extavia was based on the same registration trials as the approval for Betaseron, but a separate Biologic License Agreement (BLA) was filed by the manufacturer of Extavia. Availability of generic formulations of biologic agents, including the MS-DMDs, is unknown at this time. Extavia is supplied with a larger needle size (27 gauge vs. 30 gauge) and different packaging than Betaseron (30-day supply vs. 28-day supply). The FDA-approved indications for Extavia are the same as Betaseron.

The interferon beta-1b clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no head-to-head trials comparing interferon beta-1b (Extavia) to interferon-beta-1b (Betaseron) and there is no conclusive data to support superiority of one drug over the other. After review of the clinical literature, interferon beta-1b (Extavia) does not have compelling clinical advantages over existing MS-DMDs on the UF.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) there is currently insufficient data to conclude interferon beta-1b (Extavia) offers improved efficacy, safety, or tolerability compared to the UF product interferon beta-1b (Betaseron).

Relative Cost-Effectiveness — The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the other currently available MS-DMDs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of interferon beta-1b (Extavia). Results from the CMA showed the projected weighted average cost per day for interferon beta-1b (Extavia) is higher than the other formulary MS-DMDs, including interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), and glatiramer acetate (Copaxone).

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) interferon beta-1b (Extavia) was not cost effective relative to the other UF agents in the MS-DMDs drug class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 0 abstained, 1 absent) interferon beta-1b (Extavia) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —Based on the clinical evaluation of interferon beta-1b (Extavia) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) that no MN criteria are applicable for Extavia.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 2 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Pharmacy Benefits Program (TPHARM), and at Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Antidepressant-1s (AD-1s) — Bupropion Hydrobromide Extended Release (Bupropion HBr ER) Tablets (Aplenzin)

Relative Clinical Effectiveness — Bupropion HBr (Aplenzin) is a norepinephrine and dopamine reuptake inhibitor (NDRI) approved for the treatment of major depressive disorder (MDD) in adults. The antidepressants in the AD-1 drug class were last reviewed for UF placement in November 2005 and are comprised of the selective serotonin reuptake inhibitors (SSRIs), NDRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and the serotonin antagonist/reuptake inhibitors. Bupropion HBr ER (Aplenzin) was approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic (FDC) Act after demonstrating bioequivalence to bupropion hydrochloride (HCl) ER tablets (Wellbutrin XL). The other NDRIs on the UF are bupropion HCl immediate release (IR) (Wellbutrin IR, generics) and bupropion HCl sustained release (SR) (Wellbutrin SR, generics), with the latter designated as BCF. Bupropion HBr ER tablets are dosed daily, whereas the IR and SR formulations of bupropion HCl are dosed three times and two times daily, respectively. Inclusion of the HBr salt in Aplenzin, rather than the HCl salt included in Wellbutrin products, allows the maximum bupropion dose to be contained in one tablet.

The bupropion HBr ER (Aplenzin) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no direct comparative clinical trials between bupropion HBr ER tablets and the other NDRIs, and no trials are available that evaluate outcomes. The clinical trials used to obtain FDA approval were pharmacokinetic studies demonstrating bioequivalence to bupropion HCl

ER (Wellbutrin XL). The safety profile of bupropion HBr is based on data collected for Wellbutrin SR (bupropion hydrochloride sustained release), thus it is identical to other bupropion products.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) bupropion HBr ER tablets (Aplenzin) do not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other NDRIs currently included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the other NDRIs in the AD-1 class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of bupropion HBr ER tablets (Aplenzin) relative to other UF NDRIs. Results from the CMA showed the projected weighted average cost per day for bupropion HBr ER (Aplenzin) is higher than the bupropion HCl formulations (Wellbutrin IR, SR, and XL). The CMA also revealed the projected weighted average cost per day for bupropion HBr ER tablets (Aplenzin) is higher than the formulary NDRI, bupropion HCl 12-hour formulation (Wellbutrin SR) and the non-formulary 24-hour formulation (Wellbutrin XL).

Relative Cost-Effectiveness Conclusion —The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) that bupropion HBr ER tablets (Aplenzin) are not cost effective relative to other AD-1 NDRIs included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 0 opposed, 2 abstained, 0 absent) that bupropion HBr ER tablets (Aplenzin) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —

Based on the clinical evaluation of bupropion HBr ER tablets (Aplenzin) and the conditions for establishing MN of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) that no MN criteria are applicable for Aplenzin.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. Antidepressant-1s (AD-1s) — Milnacipran Tablets (Savella)

Relative Clinical Effectiveness — Milnacipran (Savella) is an SNRI approved for the treatment of fibromyalgia in adults. The agents in the AD-1 drug class were last reviewed for UF placement in November 2005. The other SNRIs on the Uniform Formulary are venlafaxine immediate-release tablets (Effexor, generics), venlafaxine extended release capsules (Effexor XR), and venlafaxine extended-release tablets (no brand name). The UF also includes other drugs medically accepted to treat fibromyalgia, including several selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressant (TCA) amitriptyline (Elavil, generics) and cyclobenzaprine (Flexeril, generics). Milnacipran is approved for depression outside of the US, but the manufacturer will not seek FDA approval for depression.

The milnacipran (Savella) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). In clinical trials, milnacipran significantly improved a composite of fibromyalgia symptoms when compared to placebo. There are no direct comparative clinical trials between milnacipran and the other medications FDA-approved or used off-label for the management of fibromyalgia. Meta-analyses have shown efficacy for use of the antidepressants (SSRIs and TCAs) and cyclobenzaprine in treating fibromyalgia. After review of the clinical literature, milnacipran (Savella) does not have compelling clinical advantages over existing fibromyalgia therapies on the UF. There is currently insufficient data to conclude that milnacipran (Savella) offers improved efficacy, safety, or tolerability compared to other SNRIs or other drugs medically accepted for the treatment of fibromyalgia.

Other Factors — The Pharmacy Outcomes Research Team (PORT) reported results of an analysis comparing the relative frequency of ICD-9 diagnosis codes indicative of fibromyalgia; nerve disorders including phantom limb syndrome, carpal tunnel, peripheral neuropathy, diabetes with neurological symptoms, and postherpetic neuralgia (neuropathic pain); depression; or seizure disorder, among patients receiving SNRIs (duloxetine or venlafaxine), GABA analogs (pregabalin or gabapentin), or the SSRI citalopram.

Study patients (n=20,271) comprised a 10% random sample of all patients who received a prescription for any of these medications at any DoD pharmacy point of service in March 2009. All ICD-9 diagnosis codes were collected for these patients over a 21-month period (1 Oct 07 – 30 Jun 09) from purchased and direct care medical claims data (inpatient and outpatient) in the MHS Data Mart (M2). A second, separate analysis using the same methods examined ICD-9 coding among a 10% sample of patients who received a tricyclic antidepressant (TCA) or cyclobenzaprine in March 2009 (n=10,866).

Pertinent results included:

- The percentage of patients with a ICD-9 diagnosis code for fibromyalgia (729.1) was highest among patients with prescriptions for the two agents with FDA-approved indications for fibromyalgia, pregabalin (30%) and duloxetine (26%), followed by 15% with gabapentin, 11% with venlafaxine, and 7% with citalopram. A total of 14% of patients with prescriptions for a TCA or cyclobenzaprine had ICD-9 codes for fibromyalgia.
- ICD-9 codes consistent with neuropathic pain occurred most commonly among patients with prescriptions for pregabalin (50%) or gabapentin (44%), followed by 29%, 15%, and 13% of patients with prescriptions for duloxetine, venlafaxine, or citalopram, respectively.
- A diagnosis of depression was noted in more than half of patients with prescriptions for duloxetine (54%) or venlafaxine (52%), followed by citalopram (47%), pregabalin (28%), and gabapentin (24%).

- A high percentage of patients with ICD-9 codes for fibromyalgia also had ICD-9 codes for depression, ranging from 71% of patients with prescriptions for citalopram to about 40% with gabapentin or pregabalin. A smaller but still substantial percentage of patients with ICD-9 codes for neuropathic pain also had ICD-9 codes for depression (25 to 60%).
- ICD-9 codes for seizure disorder ranged between 2-3% for any study medication.

While this analysis had clear limitations (including the inability to link diagnosis codes with the actual reason for use), the Committee agreed that it was unlikely that fibromyalgia represents the most common use for any study medication. Taken together with milnacipran's regulatory approval and use for depression outside the U.S. and multiple uses for other agents with a fibromyalgia indication, the Committee did not feel that the results supported consideration of a separate drug class for fibromyalgia, even given milnacipran's lack of any other FDA-approved indication. Several Committee members commented that logically such a grouping of agents should also contain the TCAs (particularly amitriptyline) and cyclobenzaprine, which have a substantial body of evidence supporting first-line use for fibromyalgia.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that despite its FDA-approved status, milnacipran is one of many available treatments for fibromyalgia. Milnacipran (Savella) does not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other SNRIs and medically-accepted drugs used for fibromyalgia currently included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of milnacipran (Savella) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other SNRIs in the AD-1 class, as well as other medically-accepted treatments for fibromyalgia. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of milnacipran (Savella) relative to other UF SNRIs and medically-accepted treatments for fibromyalgia. Results from the CMA showed the projected weighted average cost per day for milnacipran (Savella) is higher than the UF alternatives commonly used to treat fibromyalgia, including the tricyclic antidepressant amitriptyline (Elavil, generics) and cyclobenzaprine (Flexeril, generics).

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) that

milnacipran (Savella) is not cost effective relative to other medically-accepted drugs for the management of fibromyalgia included on the UF.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 1 opposed, 1 abstained, 0 absent) that milnacipran (Savella) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —Based on the clinical evaluation of milnacipran (Savella) and the conditions for establishing MN of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) MN criteria. (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. Overactive Bladder Drugs (OABs) — Oxybutynin Topical Gel (Gelnique)

Relative Clinical Effectiveness — Oxybutynin chloride 10% topical gel (Gelnique) is an antimuscarinic agent classified as an overactive bladder (OAB) drug. It is the second topical oxybutynin product to reach the market, following the transdermal patch (Oxytrol). Like the other OAB drugs, Gelnique is FDA-approved for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency. Gelnique is a clear and colorless hydroalcoholic gel available in a 1 gram sachet (1.14 mL) unit dose that contains 100 mg oxybutynin chloride, which is estimated to deliver approximately 4 mg of oxybutynin chloride per day. The OAB drug class was previously reviewed for UF placement in August 2008 and February 2006. Other oxybutynin products are included on the UF (oxybutynin immediate release (IR) and sustained release (SR) tablets [Ditropan, Ditropan SR, generics] and the Oxytrol patch).

The oxybutynin 10% gel (Gelnique) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no comparative clinical trials between Gelnique and the other OAB drugs, and no published trials evaluating outcomes other than changes in signs and symptoms of OAB. The clinical trials used to obtain FDA approval reported Gelnique was effective at reducing the number of incontinence episodes per day, number of urinary frequency episodes per day, and increasing the urinary volume per void in patients with OAB, comparable to the other OAB agents. The safety profile of Gelnique appears to be comparable to other OAB agents.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that oxybutynin 10% gel (Gelnique) did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over other OAB agents included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the anticholinergic agents in the overactive bladder (OAB) class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of oxybutynin 10% gel (Gelnique) relative to other UF anticholinergic OAB agents. Results from the CMA showed the projected weighted average cost per day for oxybutynin 10% gel (Gelnique) is higher than the other formulary OAB anticholinergic agents, including extended-release oral agents (oxybutynin ER [Ditropan XL] and tolterodine ER [Detrol LA]), and the UF transdermal patch formulation (Oxytrol).

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) that oxybutynin 10% gel (Gelnique) is not cost effective relative to the other UF anticholinergic agents in the OAB class.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 1 opposed, 0 abstained, 1 absent) oxybutynin 10% gel (Gelnique) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** — Based on the clinical evaluation for oxybutynin 10% gel (Gelnique) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 0 abstained, 2 absent) MN criteria for oxybutynin 10% gel (Gelnique). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 2 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

E. Narcotic Analgesics — Tapentadol Tablets (Nucynta)

Relative Clinical Effectiveness — Tapentadol (Nucynta) is an oral, centrally acting, synthetic opioid analgesic, indicated for the relief of moderate to severe acute pain in adults. It is a Schedule II controlled substance and classified as an immediate release, single component high potency agent in the narcotic analgesic drug class, which was last reviewed for UF in February 2007. Tapentadol's exact mechanism of action is unknown, but analgesia is potentially conferred by mu-agonist activity and inhibition of norepinephrine reuptake. It has no pharmacologically active metabolites and requires multiple daily dosing.

The clinical evaluation for tapentadol included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). The pivotal trials used to obtain FDA approval reported that tapentadol was superior to placebo, and non-inferior at specific doses to oxycodone immediate release (IR) in relieving pain in patients with end-stage joint disease or following bunionectomy. There are no published direct comparative trials between tapentadol and other narcotic analgesics. The safety profile of tapentadol reflects that of other narcotic analgesics on the UF, with the exception of a lower incidence of constipation observed in clinical trials compared to immediate-release oxycodone.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that although tapentadol may result in less gastrointestinal adverse events compared to oxycodone IR, this was an irrelevant benefit given its current indication for short-term therapy in the treatment of acute pain. There is insufficient evidence to suggest a clinically meaningful therapeutic advantage in patient outcomes, in terms of efficacy and safety, compared to the other narcotic analgesics already on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of tapentadol in relation to the efficacy, safety, tolerability, and clinical outcomes of the other immediate release, single component high potency agents in the narcotic analgesic drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of tapentadol (Nucynta) relative to other UF scheduled and non-scheduled agents in the narcotic analgesic class. Results from the CMA showed the projected weighted average

cost per day for tapentadol (Nucynta) is higher than the other formulary immediate release, single component high potency agent in the narcotic analgesic drug class, including morphine sulfate IR oral, oxycodone hydrochloride IR, and tramadol hydrochloride IR formulations.

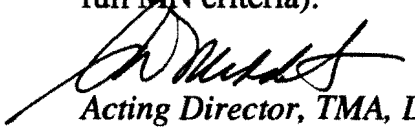
Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) that tapentadol (Nucynta) is not cost effective relative to the other immediate release, single component high potency agents in the narcotic analgesic drug class

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 0 absent) tapentadol (Nucynta) be designated non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the determination that morphine sulfate (MS-IR/generic; MS-Contin/generic) remains the most cost-effective narcotic analgesic on the UF compared to tapentadol (Nucynta).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —Based on the clinical evaluation of tapentadol (Nucynta) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) MN criteria for tapentadol (Nucynta). (See Appendix B for full MN criteria).



Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** —
The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

F. Narcotic Analgesics — Tramadol Extended Release (ER) Tablets (Ryzolt)

Relative Clinical Effectiveness — Tramadol extended-release (ER), (Ryzolt) is an oral centrally acting analgesic, and is classified as an extended release, single component, low-potency agent in the narcotic analgesic drug class; it is not a controlled drug. Ryzolt has the same active ingredient as Ultram IR and Ultram ER, but with a differing mode of delivery, and was approved under section 505(b)(2) of the FDC. Ryzolt exhibits immediate-release and extended-release properties, due to its dual-matrix delivery system.

Tramadol ER is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. The postulated mechanism for analgesic efficacy of tramadol is a combination of mu-agonist activity and weak inhibition of serotonin and norepinephrine reuptake. The clinical evaluation for Ryzolt included, but was not limited to the requirements stated in the UF rule, 32 CFR 199.21(e)(1).

In three out of four pivotal trials, Ryzolt was unable to demonstrate superiority over a comparator. The study on which approval was based showed questionable efficacy over placebo. No direct comparative trials have been conducted between Ryzolt and other tramadol products available in the US or other narcotic analgesics. The safety profile of Ryzolt reflects that of other tramadol products on the UF.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that although Ryzolt offered a novel delivery mechanism, there was insufficient evidence to suggest a clinically meaningful

therapeutic advantage in terms of efficacy and safety, compared to the other tramadol products available on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of the tramadol ER in relation to the efficacy, safety, tolerability, and clinical outcomes of the other extended release, single component low-potency agents in the narcotic analgesic drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of tramadol ER (Ryzolt) relative to the other UF chemically identical chronic pain agents. Results from the CMA showed the projected weighted average cost per day for tramadol ER (Ryzolt) is higher than the non-formulary low-potency single analgesic agent, tramadol extended-release (Ultram ER) and significantly higher than the formulary product tramadol immediate-release (Ultram/generics) Results from the CMA showed the projected weighted average cost per day for tramadol ER (Ryzolt) is higher than the non-formulary low-potency single analgesic agent, tramadol extended release (Ultram ER) and significantly higher than the formulary product tramadol immediate release (Ultram/generics).

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) that tramadol ER (Ryzolt) is not cost effective relative to tramadol extended-release (Ultram ER).

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 0 abstained, 1 absent) tramadol ER tablets (Ryzolt) be designated non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the determination that Ultram (tramadol IR) remains the most cost effective low-potency single narcotic agent on the UF compared to Ryzolt (tramadol ER).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —Based on the clinical evaluation of Ryzolt (tramadol ER) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) MN criteria for Ryzolt (tramadol ER). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

G. Renin Angiotensin Aldosterone Antihypertensive Agents (RAAs) — Valsartan/Amlodipine/Hydrochlorothiazide (HCTZ) Tablets (Exforge HCT)

Relative Clinical Effectiveness — Exforge HCT is a fixed-dose combination product containing valsartan (Diovan), amlodipine (Norvasc, generics), and hydrochlorothiazide (HCTZ, generics). It is the first three-drug combination product approved for hypertension and contains an angiotensin receptor blocker (ARB; Diovan), a dihydropyridine calcium channel blocker (DHP CCB; amlodipine), and a diuretic (HCTZ). Valsartan/amlodipine/hydrochlorothiazide is solely indicated for treating hypertension. Valsartan (Diovan) and the combination product valsartan/amlodipine (Exforge) are currently designated as non-formulary on the UF; amlodipine (Norvasc, generics) and HCTZ are BCF products. Exforge HCT is included in the renin-angiotensin antihypertensive agents (RAAs) UF drug class, which is comprised of several sub-classes (ARBs, angiotensin converting enzyme (ACE) inhibitors, direct

renin inhibitors and their combinations with CCBs or HCTZ).

Treatment with Exforge HCT has been shown in one randomized trial to produce additive BP lowering and superior BP control compared to combinations of the individual components administered as pairs.

The adverse event profile of valsartan/amlodipine/HCTZ is similar to that of the individual ARB, DHP CCB, and diuretic components. In the clinical trial, the incidence of dizziness (7%) was higher among patients taking the three-drug combination than with any of two-drug combinations, resulting in a 0.7% study drop-out rate, which is less than that seen in a typical ACE inhibitor trial. Hypokalemia was less frequent among participants who took a combination that included the ARB and diuretic than among those who took a combination that included a diuretic without an ARB. Peripheral edema was less common among participants who took a combination that included an ARB and a DHP CCB than among those who took a combination that included a DHP CCB without an ARB.

Studies specifically evaluating patient compliance (adherence and persistence) using Exforge HCT have not been conducted. Nevertheless, there is significant evidence that adherence (short-term compliance) and persistence (long-term compliance) are improved 10–15% for each tablet reduced. That is, both measures of compliance improve 15% when reducing from three tablets to two, and improve 10% when reducing two tablets to one. No study has been conducted addressing reduction of three tablets to one.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that, while valsartan/amlodipine/HCTZ (Exforge HCT) does not have a significant, clinically meaningful therapeutic advantage in terms of safety or efficacy over other antihypertensive combinations/agents included on the UF, the benefits it offers in terms of improved compliance, via decreased tablet burden and simplified medication regimen, are clinically significant.

Relative Cost-Effectiveness — The P&T Committee evaluated the cost of valsartan/amlodipine/HCTZ (Exforge HCT) in relation to the efficacy, safety, tolerability, and clinical outcomes of the antihypertensive agents in the RAAs UF drug class as single ingredient agents and combination formulations. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of Exforge HCT relative to other UF RAAs. Results from the CMA showed the projected weighted average cost per day for amlodipine/valsartan/HCTZ (Exforge HCT) is higher than multi-tablet combinations of the other formulary RAAs, including

amlodipine tablets with lisinopril/HCTZ (Prinzide, generics), telmisartan/HCTZ (Micardis HCT), aliskiren/HCTZ (Tekturna HCT) and losartan/HCTZ (Hyzaar).

Relative Cost-Effectiveness Conclusion — The P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) that amlodipine/valsartan/HCTZ (Exforge HCT) is cost effective relative to the other single ingredient or combination agents in the RAAs drug class. After extensive discussion, the P&T Committee determined that the minimal extra daily cost for the amlodipine/valsartan/HCTZ (Exforge HCT) single tablet formulation was offset by the added patient convenience, and may clinically improve patient compliance.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (4 for, 11 opposed, 0 abstained, 1 absent) against recommending that valsartan/amlodipine/HCTZ (Exforge HCT) be designated as non-formulary on the UF, thus Exforge HCT will retain uniform formulary status.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: BCF RECOMMENDATION*** — The P&T Committee considered the BCF status of valsartan/amlodipine/HCTZ (Exforge HCT). Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 0 abstained, and 1 absent) to recommend Exforge HCT not be added to the BCF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UNIFORM FORMULARY DRUG CLASS REVIEWS

A. Phosphodiesterase-5 (PDE5) Inhibitors for Pulmonary Arterial Hypertension (PAH)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the Phosphodiesterase Type-5 (PDE-5) inhibitors for the treatment of pulmonary arterial hypertension (PAH). Sildenafil (Revatio) was previously reviewed for UF placement in August 2005. Tadalafil (Adcirca) is the second PDE-5 inhibitor FDA-approved for PAH, and was recently launched in August 2009. Sildenafil and tadalafil are FDA-approved for treating erectile dysfunction (ED), under the trade names of Viagra and Cialis, respectively. Information regarding the safety, effectiveness, and clinical outcomes of the PAH subclass of the PDE-5 inhibitors was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

Military Health System (MHS) expenditures for the PDE-5 inhibitors for PAH exceeded $400,000 per month at the retail, mail order and MTFs points of service from September 2007 to September 2009. In the MHS, sildenafil (Revatio) is the highest utilized PDE-5 inhibitor for PAH, with approximately 500 prescriptions dispensed monthly. There have been less than 60 unique utilizers of Adcirca, since its market launch in August 2009.

Relative Clinical Effectiveness Conclusion — The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding PDE-5 inhibitors for PAH:

1. With regard to efficacy, the following conclusions were made:
    a) Sildenafil (Revatio) and tadalafil (Adcirca) are FDA-approved to improve exercise ability in patients with PAH. Sildenafil has an additional indication specifically to delay clinical worsening in patients with PAH when used in combination with background intravenous epoprostenol (Flolan).
    b) There are no head-to-head trials comparing the two PDE-5 inhibitors for PAH. However, sildenafil and tadalafil show similar improvements in 6-minute walking distance (6MWD) when indirect comparisons of clinical trial results that incorporated the FDA-approved dosing regimens are made.
    c) Sildenafil and tadalafil delay the time to clinical worsening of disease, which is defined variously as a composite of death, transplantation, hospitalization for PAH, initiation of new therapy, or worsening functional class.
        (1) A clinically significant delay in the time to clinical worsening with sildenafil was shown in one trial that used doses four times higher than the FDA-approved dose, and used adjunctive IV epoprostenol treatment in all the patients.

(2) Tadalafil was shown to delay the time to clinical worsening of PAH in one trial that used FDA-approved dosing and used adjunctive bosentan (Tracleer) therapy in 55% of the patients.

d) There is insufficient evidence to conclude that there are clinically relevant differences in clinical effectiveness of PDE-5 inhibitors for PAH.

2. With regards to safety and tolerability, the P&T Committee agreed that there is insufficient evidence to conclude there are clinically relevant differences in safety between PDE-5 inhibitors for PAH. The product labeling for the two drugs is similar with regard to contraindications, precautions, and warnings, and reflects the safety section found in the package inserts for the ED products Viagra and Cialis. The sildenafil and tadalafil doses used for PAH treatment are associated with an increased incidence of adverse events (headache, flushing, myalgia), than occurs with the doses used in ED. Headache is the most frequently reported adverse event with Revatio and Adcirca.
3. With regards to other factors, generic availability of sildenafil (Viagra and Revatio trade names) is expected in 2012, compared to 2020 for tadalafil (Cialis and Adcirca). Additionally, the P&T Committee recognized the convenience to the patient with the once daily dosing required with Adcirca, in contrast to the 3-times daily dosing needed with Revatio. Sildenafil and tadalafil require Prior Authorization when used for PAH (*see* August 2009 DoD P&T Committee meeting minutes for full PA criteria for the PDE-5 inhibitors).

Relative Cost-Effectiveness —The P&T Committee evaluated the costs of sildenafil (Revatio) and tadalafil (Adcirca) in relation to the efficacy, safety, tolerability, and clinical outcomes of the PDE-5 inhibitors for PAH. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). CMA and Budget Impact Analysis (BIA) were used to evaluate the cost effectiveness of the PDE-5 inhibitors for PAH.

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) that:

1. Results from the CMA of PDE-5 inhibitors for PAH agents revealed that sildenafil (Revatio) is the most cost effective PDE-5 inhibitor for PAH agent based on an analysis of the cost per day of treatment. Cost per day of therapy was calculated using average daily consumption rates for sildenafil (Revatio) and tadalafil (Adcirca).
2. Budget impact analysis (BIA) was used to evaluate the potential impact of scenarios with selected PDE-5 inhibitor agents designated formulary or non-formulary on the UF. Results from the BIA of PDE-5 inhibitors for PAH

revealed that placing sildenafil citrate (Revatio) on the UF was the most cost effective scenario overall.

3. The results of the BIA showed that tadalafil (Adcirca) is more costly than sildenafil (Revatio) in all scenarios evaluated.

1. ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 1 absent):

   a) Sildenafil (Revatio 20 mg) remain classified as formulary on the UF.

   b) Tadalafil (Adcirca 20 mg) be designated as non-formulary under the UF, based on cost effectiveness.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —

   Based on the clinical evaluation of tadalafil (Adcirca) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) MN criteria for tadalafil (Adcirca). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 1 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

IV. UTILIZATION MANAGEMENT — UF/BCF ADDITIONS/DELETIONS

A. Status of Bupropion HCl ER Tablets (Wellbutrin XL) on the UF

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to determine whether the UF status of agents designated as non-formulary needs to be readdressed. The P&T Committee reevaluated the UF status of bupropion ER (Wellbutrin XL, generics) in light of recent price reductions in the generic 150 mg and 300 mg formulations across all three points of service.

Clinical Effectiveness Conclusion — The AD-1 agents were evaluated for UF status at the November 2005 meeting. At that meeting, the P&T Committee concluded bupropion appears similar in efficacy to SSRIs; its major advantage is a lower incidence of sexual adverse effects than the other AD-1 agents. The major disadvantages are the risk of seizures at high doses and its tendency to produce activation/agitation. The putative advantage of the once-daily ER formulation (Wellbutrin XL) is increased compliance, although clinical trial data assessing compliance is not available.

Cost Effectiveness Conclusion — The P&T Committee agreed that the generic bupropion ER (Wellbutrin XL) formulations were now cost effective at all three points of service.

1. ***COMMITTEE ACTION: UF DECISION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 0 absent) that bupropion ER (Wellbutrin XL, generic) be immediately reclassified as generic on the UF. Wellbutrin XL was included on the "list of non-formulary drugs for re-evaluation of UF status" presented to the Beneficiary Advisory Panel in January 2008 and approved by the Director, TMA on 13 February 2008. No further approval is needed.

VI. BASIC CORE FORMULARY ISSUES

A. Levonorgestrel — BCF Addition

The Committee received a request to reconsider BCF addition of levonorgestrel (Plan B, generics). Levonorgestrel is currently designated as formulary on the UF; it was originally reviewed for UF status as part of the contraceptive drug class in May 2006. Since the original UF class review, levonorgestrel is now available in a generic product under the trade name Next Choice, which contains two 0.75 mg tablets, taken 12 hours apart for emergency contraception. The Plan B product has been voluntarily discontinued by the manufacturer as of June 2009. A new product, Plan B One Step, is marketed that contains one 1.5 mg tablet, taken in a single dose. Studies evaluating the two tablets vs. one tablet products reported no clinically relevant differences between the regimens in the pharmacokinetic profiles, number of resulting pregnancies, or incidence of nausea and vomiting. The American College of Obstetrics and Gynecology recommends a single dose of 1.5 mg levonorgestrel as one option, or two doses of levonorgestrel 0.75 mg taken 12–24 hours as another option for emergency contraception.

Plan B, Next Choice, and Plan B One Step do not require a prescription for patients 17 years of age and older, thus they are not available from the TPHARM, since they are over-the-counter products for this age group. A prescription is required for patients younger than 17 years; the products are available from the TPHARM if a prescription is supplied. A quantity limit of one fill per prescription, with no refills applies at the TPHARM. Each of the three military services has a policy supporting availability of emergency contraception at the MTFs. A cost analysis between Next Choice and Plan B One Step found Next Choice as the more cost effective product. After reviewing the clinical and cost effectiveness of the product, the P&T Committee agreed that levonorgestrel should be placed on the BCF.

1. ***COMMITTEE ACTION: BCF ADDITION*** — The Committee voted (13 for, 2 opposed, 0 abstained, 1 absent) to recommend adding levonorgestrel 0.75 mg (Next Choice; generic Plan B) to the BCF immediately upon signing of the November 2009 meeting minutes. Plan B One Step would remain designated as formulary under the UF. The current quantity limits of one fill per prescription, with no refills, remains.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Hydrocodone/Acetaminophen 5 mg/500 mg — BCF Deletion

The P&T Committee received a request from the field to re-examine the BCF status of hydrocodone/acetaminophen (Vicodin, generics). Recent FDA communications

outline the potential for accidental ingestion of excessive acetaminophen (Tylenol, generics) doses and a proposed black box warning for prescription products that combine acetaminophen with another drug. Several prescription and OTC products contain acetaminophen, which increases the risk of inadvertent ingestion of higher than maximally recommended dose, and the potential for resulting hepatic injury. Administering hydrocodone/acetaminophen 5mg/500 mg at the highest recommended dose and dosing interval results in an acetaminophen dose that exceeds the maximal FDA-approved dose.

1. ***COMMITTEE ACTION: BCF DELETION*** — The Committee voted (11 for, 3 opposed, 0 abstained, 2 absent) to delete hydrocodone/acetaminophen 5mg/500 mg from the BCF immediately upon signing of the November 2009 meeting minutes; it will remain formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. Telmisartan +/- HCTZ (Micardis, Micardis HCT) — BCF Deletion

The ARBs and ARB combinations with HCTZ were last reviewed for UF placement in May 2007. Since the last review, the ARB +/- HCTZ combinations have been categorized into a larger class, the Renin-Angiotensin Antihypertensives (RAAs), which is comprised of the angiotensin converting enzyme inhibitors (ACEs +/- HCTZ), the ARB combinations with CCBs, the direct renin inhibitors +/- HCTZ, and the ARB/CCB/HCTZ combinations. The existing preferential pricing for the current BCF ARB, telmisartan +/- HCTZ (Micardis, Micardis HCT) has been terminated by the manufacturer, effective Jan 2010. Additionally in 2010, generic competition in the class is expected, and updated hypertension treatment guidelines from the Joint National Commission will be released. The RAAs drug class will be reviewed for UF status at an upcoming meeting. Due to the aforementioned developments, the Committee recommended deleting telmisartan +/- HCTZ from the BCF.

1. ***COMMITTEE ACTION: BCF DELETION*** — The Committee voted (15 for, 0 opposed, 0 abstained, 1 absent) to delete telmisartan +/- HCTZ (Micardis, Micardis HCT) from the BCF immediately upon signing of the November 2009 DoD P&T Committee minutes; it will remain formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VII. NATIONAL DEFENSE AUTHORIZATION ACT (NDAA) SECTION 703 — INCLUSION OF TRICARE RETAIL PHARMACY PROGRAM IN FEDERAL PROCUREMENT OF PHARMACEUTICALS UPDATE

A. Medical Necessity for August 09 Section 703 Recommendations —

The committee reviewed medical necessity criteria for drugs that were not included on a Department of Defense Retail Refund Pricing Agreement at the August 2009 meeting. These drugs are not compliant with FY2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated non-formulary under the Uniform Formulary and will require a pre-authorization prior to use in the retail point of service (POS) and medical necessity in military treatment facilities. These non-formulary drugs will remain available in the mail order POS without pre-authorization. Pre-authorization was determined at the November 2009 DoD P&T Committee meeting. Drugs with and without pricing agreements were systematically classified based along therapeutic and pharmacologic lines. The classification system was based on the American Hospital Formulary System Classification and First Data Bank classification. See Appendix C for the full list of affected medications.

1. ***COMMITTEE ACTION — DRUGS GENERICALLY AVAILABLE REQUIRING PRIORI-AUTHORIZATION:*** The P&T Committee voted (15 for, 0 against, 0 abstained, 1 absent) to recommend the drugs listed in Appendix C, Section A follow the standard TRICARE rules for brand-generic prior-authorization criteria.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION — MEDICAL NECESSITY CRITERIA:*** The P&T Committee voted (13 for, 0 against, 0 abstained, 3 absent) to recommend medical necessity criteria for the drugs listed in Appendix C, Section B.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION — IMPLEMENTATION DATE FOR MEDICAL NECESSITY:*** The P&T Committee voted (13 for, 0 against, 0 abstained, 3 absent) to recommend the implementation date will not be prior to 1 April 2010 and not later than 180 days after the minutes of this meeting are signed.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION — TRANSITION DATE AT THE MTF POS:*** The P&T Committee voted (13 for, 0 against, 0 abstained, 3 absent) to recommend a transition period at the MTF POS as ending no later than 1 January 2011.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Drug Non-compliant with NDAA Section 703 The P&T Committee reviewed drugs that were not included on a DoD Retail Refund Pricing Agreement. These drugs are not compliant with FY08 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated non-formulary on the UF and will require a pre-authorization prior to use in the retail point of service (POS) and medical necessity in MTFs. These non-formulary drugs will remain available in the mail order POS without pre-authorization. Pre-authorization will be determined at the February 2010 DoD P&T Committee meeting. Drugs with and without pricing agreements were systematically classified based along therapeutic and pharmacologic lines. The classification system was based on the American Hospital Formulary System Classification and First Data Bank classification. See Appendix D for the full list of affected medications.

1. ***COMMITTEE ACTION — DRUGS RETAINING UF STATUS:*** The P&T Committee voted (12 for, 0 against, 0 abstained, 4 absent) to recommend the drugs listed in Appendix E, Section A to retain formulary status on the Uniform Formulary.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2. ***COMMITTEE ACTION — DRUGS RETAININ OR DESIGNATED AS NON-FORMULARY:*** The P&T Committee voted (12 for, 0 against, 0 abstained, 4 absent) to recommend the drugs listed in Appendix E, Section B to retain non-formulary status or be designated non-formulary on the Uniform Formulary.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3. ***COMMITTEE ACTION — IMPLEMENTATION DATE FOR PRE-AUTHORIZATION:*** The P&T Committee voted (12 for, 0 against, 0 abstained, 4 absent) to recommend the implementation date will not be prior to 1 April 2010 and not later than 180 days after the minutes of this meeting are signed. Formulary status of a drug in these lists will revert back to previous formulary status if Price Agreements are received prior to 1 February, 2010.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4. ***COMMITTEE ACTION — TRANSITION DATE AT THE MTF POS:*** The P&T Committee voted (12 for, 0 against, 0 abstained, 4 absent) to recommend a transition period at the MTF POS as ending no later than 1 January 2011.

Acting Director, TMA, Decision: ☒Approved ☐ Disapproved

Approved, but modified as follows:

VIII. CLASS OVERVIEWS

Class overviews for the Basal Insulins and the RAAs were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed at an upcoming meeting.

IX. ADJOURNMENT

The meeting adjourned at 1700 hours on 5 November 2009 and at 1100 hours on 6 November 2009. The next meeting will be in February 2010.

Appendix A — Attendance

Appendix B — Table of Medical Necessity Criteria for Newly Approved Drugs

Appendix C — Table of Medical Necessity for August 09 Section 703 Recommendations

Appendix D — National Defense Authorization Act (NDAA)-Section 703 Affected Medications

Appendix E — Table of Implementation Status of UF Recommendations/Decisions –

Appendix F — Table of Abbreviations

SUBMITTED BY:

CDR James Ellzy, MC, USN
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Allen W. Middleton
Acting Director

3 Feb 2010
(Date)

Appendix A — Attendance

Voting Members Present	
CDR James Ellzy, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director, DoD Pharmacoeconomic Center, (Recorder)
Lt Col Thom Bacon *for Col Everett McAllister, MSC*	Chief, Pharmaceutical Operations Directorate
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
Capt Walter Downs, MC	Navy, Internal Medicine Physician
CAPT David Tanen, MC	Navy, Physician at Large
Lt Col Mike Spilker, BSC	Consultant to the AF/SG
Lt Col Brian Crownover, MC	Air Force, Physician at Large
CDR Phil Blaine *for CAPT Stephanie Simon, MSC*	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician, Alternate
LTC Bruce Lovins, MC	Army, Family Practice Physician, Alternate
LTC Douglas Louggee for COL Ted Cieslak, MC	Army, Physician at Large
COL Peter Bulatao *for COL Carole Labadie, MSC*	Army, Pharmacy Officer, Alternate
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino	Department of Veterans Affairs
Voting Members Absent	
COL Carole Labadie, MSC	Army, Pharmacy Officer
CAPT Stephanie Simon, MSC	Navy Pharmacy Officer
COL Ted Cieslak, MC	Army, Physician at Large
Col Everett McAllister BSC	Chief, Pharmaceutical Operations Directorate
Nonvoting Members Present	
Mr. David Hurt	Assistant General Counsel, TMA
Nonvoting Members Absent	
COL Kent Maneval, MS	Defense Medical Standardization Board
Mr. William Davies	TRRx/TMOP COR
Guests	
CDR Michael Lee	Indian Health Service
Dr. Lisa Longo	VA PBM
Ms. Melanie Richardson	DoD Pharmacy Operations Directorate

Appendix A — Attendance (continued)

Others Present	
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center
LCDR Bob Selvester, MC	DoD Pharmacoeconomic Center
CAPT Brian Haney, MC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
HM2 Trishonya McMihelk	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Roger Potyk	DoD Pharmacy Outcomes Research Team contractor
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor

Appendix B — Table of Medical Necessity Criteria for Newly Approved Drugs

Drug / Drug Class	Medical Necessity Criteria
Tadalafil tablets (Adcirca) **Phosphodiesterase-5 (PDE-5) Inhibitors for Pulmonary Arterial Hypertension (PAH)**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure
Interferon Beta 1-b injection (Extavia) **Multiple Sclerosis - Disease Modulating Drugs (MS-DMDs)**	• None of the medical necessity criteria apply; interferon Beta 1-b injection (Betaseron brand name) is on the UF
Milnacipran tablets (Savella) **Antidepressant -1s (AD-1s)**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk
Bupropion hydrobromide extended release tablets (Aplenzin) **Antidepressant -1s (AD-1s)**	• None of the medical necessity criteria apply; Bupropion HCl ER (Wellbutrin XL generic) is now recommended for UF status
Oxybutynin topical gel (Gelnique) **Overactive Bladder (OAB)**	• The patient has experienced significant adverse effects from formulary alternatives.
Tapendatol tablets (Nucynta) Tramadol ER (Ryzolt) **Narcotic Analgesics**	• Use of formulary alternatives is contraindicated

Appendix C — Table of Medical Necessity and Branded Drugs with Formulary Equivalents for August 09 Section 703 Recommendations

Brand Name	Generic Name
Aclovate	aclomethasone diproprionate
Altace	ramipril
Carnitor, Carnitor SF	levocarnitine tablets, solution
Cutivate	fluticasone propionate
Cytoxan	cyclophosphamide
Depakene	valproic acid
Kaon-CL	potassium chloride
Mobic	meloxicam
Omnicef	cedinir capsules, suspension
Persantine	dipyridamole
Pletal	cilostazol
Septra;Septra DS	trimethoprim/sulfamethoxazole
Silvadene	silver sulfadiazine
Tapazole	methimazole
Temovate	clobetasol
Viroptic	trifluridine
Zonegram	zonisamide

Appendix C — Table of Medical Necessity and Branded Drugs with Formulary Equivalents for August 09 Section 703 (continued)

Drug	Generic Alternative	Brand Alternative	Applicable MN Rules
APTIVUS			1,2,3,4,5
ATROVENT HFA		Spiriva Inhaler	1,2,3,4
CORGARD	Atenolol, Metoprolol		1,2,4
CYTOMEL	Levothroid, Levothyroxine tables	Armour Thyroid	1,2,3,4,5
ELESTRIN	Estradiol Patch	Estrogel Gel, Divigel Gel, Evamist Spray, Menostar Patch, Vivelle Dot Patch	1,2,4
ELIGARD	Leuprolide Acetate Kit		1,2,3,4,5
ENDOMETRIN		First-Progesterone Vaginal Suppositories, Crinone Gel	1,2,3,4
LITHOSTAT			1,2,3,4,5
MIRAPEX	Bromocriptine	Requip XL, Ropinirole	1,2,3,4
NIRAVAM	Alprazolam Tabs Generic		1,2,3
OXISTAT	Clotrimazole Cream, Ketoconazole Cream, Shampoo	Lamisil, Mentax, Halotin, Xolegel Gel	1,3
PAMINE	Methscopolamine Bromide tablets		1,2,3
PAMINE FORTE	Methscopolamine Bromide tablets		1,2,3
PAMINE FQ	Methscopolamine Bromide tablets		1,2,3
PHOSLO	Calcium Acetate Tabs	Eliphos Tabs, Renagel Tabs, Renvela Tabs	1,2,3,4
RHEUMATREX	Methotrexate dosepack		1,2,3
SALAGEN	Pilocarpine HCl Tab	Evoxac Caps	1,2,3
THALITONE	Chlorthalidone Tabs	Diuril Oral Susp	1,2,3,4
TINDAMAX			1,2,3,4,5
TRANSDERM-SCOP			1,2,3,4,5
ULTRAVATE PAC	Halobetasol cream, ointment, gel		1,
VIRAMUNE			1,2,3,4,5

1) Use of formulary alternatives is contraindicated; 2) Patient has experienced significant adverse effects from the formulary alternative; 3) The formulary agents have resulted in therapeutic failure; 4) The patient previously responded to non-formulary agent, and changing to the formulary agent would incur unacceptable risk; 5) There is no formulary alternative

Appendix D — National Defense Authorization Act (NDAA) Section 703 Affected Medications

Product Name	Definition	Manufacturer	Number of Active Patients
ARICEPT	Alzheimers medications	EISAI INC.	85107
ARICEPT ODT	Alzheimers medications	EISAI INC.	229
DILANTIN	Anticonvulsants / antimania medications	PFIZER US PHARM	512
EPIPEN	Misc respiratory medications	DEY LABS.	13232
EPIPEN JR	Misc respiratory medications	DEY LABS.	3216
FARESTON	Oral oncological agents	GTX INC.	49
HEXALEN	Oral oncological agents	EISAI INC.	18
MENOPUR	FSH/LH fertility agents	FERRING PH INC	850
MESNEX	Oral oncological agents	BAXTER HEALTHCA	6
QUALAQUIN	Antimalarials	AR SCIENTIFIC	10967
TARGRETIN	Topical antineoplastic & premalignant lesion medic	EISAI INC.	39
VANCOCIN HCL	Misc anti-infectives	VIROPHARMA INCO	3534

Product Name	Definition	Manufacturer	Number of Active Patients
ADOXA	Tetracyclines	PHARMADERM	4
ALLEGRA	2nd gen antihistamines & combos	AVENTIS PHARM	6661
ALOCRIL	Ophthalmics for allergic conjunctivitis	ALLERGAN INC.	572
AMICAR	Misc hematological agents	XANODYNE PHARM	28
ANTABUSE	Alcohol deterrants, narcotic antagonists	DURAMED/BARR	448
ARMOUR THYROID	Thyroid and antithyroid medications	FOREST PHARM	14766
AVAGE	Psoriasis medications	ALLERGAN INC.	3
AZASAN	Immunosuppressives	SALIX PHARMACEU	70
AZELEX	Acne meds	ALLERGAN INC.	3034
BANZEL	Anticonvulsants / antimania medications	EISAI INC.	125
BETAGAN	Ophthalmics for glaucoma	ALLERGAN INC.	133
BIAXIN XL	Macrolides/ketolides	ABBOTT LABS.	430
BLEPHAMIDE	Ophthalmic antibiotics & combos	ALLERGAN INC.	3106

Product Name	Subclass	Manufacturer	Number of Utilizers
BLEPHAMIDE S.O.P.	Ophthalmic antibiotics & combos	ALLERGAN INC.	1375
BRAVELLE	FSH/LH fertility agents	FERRING PH INC	130
BREVOXYL-4	Keratolytics	STIEFEL LABS.	29
BREVOXYL-8	Keratolytics	STIEFEL LABS.	20
CAFCIT	Pulmonary II agents	BEDFORD LABS	1
CAPITAL W-CODEINE	Narcotic analgesics & combos	VALEANT	229
CARDENE SR	CCBs	EKR THERAPEUTIC	80
CITRANATAL 90 DH	Prenatal vitamins	MISSION PHARM.	524
CITRANATAL DHA	Prenatal vitamins	MISSION PHARM.	893
CITRANATAL RX	Prenatal vitamins	MISSION PHARM.	111
CLARIFOAM EF	Misc topical anti-infectives	ONSET THERAPEUT	175
CLINDESSE	Vaginal anti-infectives/antiseptics	THER-RX	3672
CORZIDE	Beta blockers & HCTZ combos	KING PHARM	59
CYCLOGYL	Ophthalmics, mydriatics	ALCON LABS.	103
CYCLOSPORINE	Immunosuppressives	IVAX PHARMACEUT	12
DARVOCET A500	Narcotic analgesics & combos	XANODYNE PHARM	8
DARVOCET-N 100	Narcotic analgesics & combos	XANODYNE PHARM	140
DARVOCET-N 50	Narcotic analgesics & combos	XANODYNE PHARM	2
DARVON	Narcotic analgesics & combos	XANODYNE PHARM	5
DARVON-N	Narcotic analgesics & combos	XANODYNE PHARM	442
DENAVIR	Misc topical anti-infectives	NOVARTIS CONSUM	6954
DILANTIN	Anticonvulsants / antimania medications	PFIZER US PHARM	857
DILTZAC ER	CCBs	APOTEX CORP	59
DORAL	Sedative/hypnotics II	QUESTCOR	40
DUET STUARTNATAL	Prenatal vitamins	XANODYNE PHARM	85
E.E.S. 200	Macrolides/ketolides	ABBOTT LABS.	109
E.E.S. 400	Macrolides/ketolides	ABBOTT LABS.	38
ELDOPAQUE FORTE	Misc topical agents	VALEANT	5
ELDOQUIN FORTE	Misc topical agents	VALEANT	2
ELESTAT	Ophthalmics for allergic conjunctivitis	ALLERGAN INC.	7821
ELIMITE	Misc topical anti-infectives	ALLERGAN INC.	8931

Product Name	Category	Manufacturer	Number of Active Products
EMLA	Topical local anesthetics	APP PHARMACEUTI	2
EPIFOAM	Topical local anesthetics	ALAVEN PHARMACE	14
ERGOLOID MESYLATES	Misc cardiovascular medications	MUTUAL PHARM CO	62
ERYPED 200	Macrolides/ketolides	ABBOTT LABS.	278
ERYPED 400	Macrolides/ketolides	ABBOTT LABS.	192
ERY-TAB	Macrolides/ketolides	ABBOTT LABS.	3208
ERYTHROCIN STEARATE	Macrolides/ketolides	ABBOTT LABS.	2002
ERYTHROMYCIN	Macrolides/ketolides	ABBOTT LABS.	3457
ESGIC	Analgesic combos	FOREST PHARM	1
ESGIC-PLUS	Analgesic combos	FOREST PHARM	33
FML	Ophthalmic anti-inflammatories	ALLERGAN INC.	7446
FML FORTE	Ophthalmic anti-inflammatories	ALLERGAN INC.	362
FML S.O.P.	Ophthalmic anti-inflammatories	ALLERGAN INC.	2830
FRAGMIN	Anticoagulants	EISAI INC.	1754
GENGRAF	Immunosuppressives	ABBOTT LABS.	4
GLUCAGEN	Binders/chelators/antidotes/overdose agents	BEDFORD LABS	194
GRANULEX	Misc topical agents	UDL	190
HYCET	Narcotic analgesics & combos	XANODYNE PHARM	157
INDERAL LA	Beta blockers & HCTZ combos	AKRIMAX PHARMAC	55
KERAFOAM	Keratolytics	ONSET THERAPEUT	109
LAMICTAL ODT	Anticonvulsants / antimania medications	GLAXOSMITHKLINE	30
LAMICTAL ODT (BLUE)	Anticonvulsants / antimania medications	GLAXOSMITHKLINE	1
LAMICTAL ODT (GREEN)	Anticonvulsants / antimania medications	GLAXOSMITHKLINE	1
LAMICTAL ODT (ORANGE)	Anticonvulsants / antimania medications	GLAXOSMITHKLINE	10
LAMICTAL XR	Anticonvulsants / antimania medications	GLAXOSMITHKLINE	43
LINDANE	Misc topical anti-infectives	MORTON GROVE PH	620
LO-OVRAL-28	Contraceptives	AKRIMAX PHARMAC	16760
LORCET 10-650	Narcotic analgesics & combos	FOREST PHARM	113
LORCET PLUS	Narcotic analgesics & combos	FOREST PHARM	18
LORTAB	Narcotic analgesics & combos	UCB PHARMA	170

Product Name	Subclass	Manufacturer	Number of Mailed Patients
MAGNACET	Narcotic analgesics & combos	MALLINCKRODT BR	102
MAVIK	Renin-Angiotensin Antihypertensives (RAAs)	ABBOTT LABS.	6
MAXIDONE	Narcotic analgesics & combos	WATSON PHARMA	1
MEBARAL	Anticonvulsants / antimania medications	OVATION PHARM	40
METHYLIN ER	ADHD / narcolepsy agents	MALLINKRT PHARM	170
MIMYX	Emollients	STIEFEL LABS.	880
MONONESSA	Contraceptives	WATSON LABS	1281
NATAFORT	Prenatal vitamins	WC PROF PRODS	1
NORCO	Narcotic analgesics & combos	WATSON PHARMA	556
OCUFEN	Ophthalmic anti-inflammatories	ALLERGAN INC.	146
OCUFLOX	Ophthalmic antibiotics & combos	ALLERGAN INC.	2814
OGEN	Estrogens & estrogen/androgen combos	PHARMACIA/UPJHN	49
OPTASE	Misc topical agents	ONSET THERAPEUT	8
PACERONE	Antiarrhythmics	UPSHER SMITH	141
PERANEX HC	Topical corticosteroids/immune modulators	KENWOOD LAB.	19
PERPHENAZINE	Typical antipsychotics	SANDOZ	709
PHRENILIN FORTE	Analgesic combos	VALEANT	126
POLY-PRED	Ophthalmic antibiotics & combos	ALLERGAN INC.	16
POLYTRIM	Ophthalmic antibiotics & combos	ALLERGAN INC.	15645
PRED MILD	Ophthalmic anti-inflammatories	ALLERGAN INC.	874
PRED-G	Ophthalmic antibiotics & combos	ALLERGAN INC.	82
PRIMSOL	Sulfonamides/folate antagonists	FSC LABS	104
PROCTOCORT	Topical corticosteroids/immune modulators	SALIX PHARMACEU	17
PROCTOFOAM-HC	Topical corticosteroids/immune modulators	ALAVEN PHARMACE	601
PROGLYCEM	Binders/chelators/antidotes/overdose agents	IVAX PHARMACEUT	28
PYRIDIUM	Misc urinary agents	WC PROF PRODS	3
REPRONEX	FSH/LH fertility agents	FERRING PH INC	92
RIMSO-50	Misc urinary agents	BIONICHE PHARMA	65
ROCALTROL	Fat soluble vitamins, replacement	VALIDUS PHARMAC	7
ROSAC	Misc topical anti-infectives	STIEFEL LABS.	189
SALAGEN	Misc neurological agents	EISAI INC.	539

Product Name	Subclass	Manufacturer	Number of Months Paid
SALKERA	Keratolytics	ONSET THERAPEUT	2
STIMATE	Misc endocrine agents	CSL BEHRING LLC	223
SYNTHROID	Thyroid and antithyroid medications	ABBOTT LABS.	7516
THEO-24	Pulmonary II agents	UCB PHARMA	910
TRINESSA	Contraceptives	WATSON LABS	8405
TUSSICAPS	Cough-cold medications	MALLINCKRODT BR	1997
ULTRASE	Gastric and pancreatic enzymes	AXCAN PHARMA US	52
ULTRASE MT 12	Gastric and pancreatic enzymes	AXCAN PHARMA US	111
ULTRASE MT 18	Gastric and pancreatic enzymes	AXCAN PHARMA US	36
ULTRASE MT 20	Gastric and pancreatic enzymes	AXCAN PHARMA US	326
VICODIN ES	Narcotic analgesics & combos	ABBOTT LABS.	40
VICOPROFEN	Narcotic analgesics & combos	ABBOTT LABS.	5
VIMPAT	Anticonvulsants / antimania medications	SCHWARZ PHARMA	384
VIOKASE	Gastric and pancreatic enzymes	AXCAN PHARMA US	518
VIVACTIL	TCAs & combos	DURAMED/BARR	76
XENADERM	Misc topical agents	HEALTHPOINT MED	388
ZARONTIN	Anticonvulsants / antimania medications	PFIZER US PHARM	2
UROCIT-K*	Urinary Agent	MISSION	4

***Added to list by electronic vote Nov 16-18, 2009**

Product Name	Subclass	Manufacturer	Number of Claims Paid
CLOUD ENHANCER	Inhaler spacers	DEY LABS.	20
ADVATE	Factor VIII	BAXTER BIOSCIEN	16
ADVATE H	Factor VIII	BAXTER BIOSCIEN	29
ADVATE L	Factor VIII	BAXTER BIOSCIEN	31
ADVATE M	Factor VIII	BAXTER BIOSCIEN	40
ADVATE SH	Factor VIII	BAXTER BIOSCIEN	13
ADVATE UH	Factor VIII	BAXTER BIOSCIEN	18
BEBULIN VH IMMUNO	Factor IX preparation	BAXTER BIOSCIEN	2
EASIVENT	Inhaler spacers	DEY LABS.	1155
FEIBA VH IMMUNO	Multiple Factors	BAXTER BIOSCIEN	17
FLUOROPLEX	Topical antineoplastic & premalignant lesion medic	ALLERGAN INC.	393
HEMOFIL M	Factor VIII	BAXTER BIOSCIEN	3
HUMATE-P	Factor VII + VWF	CSL BEHRING LLC	21
HUMATE-P	Factor VII + VWF	CSL BEHRING LLC	25
PANRETIN	Topical antineoplastic & premalignant lesion medic	EISAI INC.	2
RECOMBINATE	Factor VIII	BAXTER BIOSCIEN	59
RESTASIS	Misc ophthalmic agents	ALLERGAN INC.	38760
SUBOXONE	Narcotic analgesics & combos	RECKITT BENCKIS	590
SUBUTEX	Narcotic analgesics & combos	RECKITT BENCKIS	80
TARCEVA	Antineoplastic systemic enzyme inhibitors	GENENTECH, INC.	2068
TARGRETIN	Oral oncological agents	EISAI INC.	49
TAZORAC	Psoriasis medications	ALLERGAN INC.	9690
THIOLA	Misc urinary agents	MISSION PHARM.	25
PAREMYD*	Ophthalmic	AKORN	0

***Added to list by electronic vote Nov 16-18, 2009**

Appendix E — Table of Implementation Status of UF Recommendations/Decisions

[illegible]	[illegible] Class	[illegible]	[illegible] BCF Class	[illegible]	[illegible]	[illegible]
Nov 09	Phosphodiesterase Type-5 Inhibitors for Pulmonary Arterial Hypertension subclass	**Recommended for non-formulary status Nov 09** ▪ tadalafil (Adcirca)	Now BCF for ED	**N/A** ▪ vardenafil (Levitra) is BCF for erectile dysfunction (ED)	pending approval	pending approval
Aug 09 (update; original review May 05)	Phosphodiesterase Type-5 Inhibitors	**No change to non-formulary status from May 05** Automated PA requiring trial of vardenafil (Levitra) applies to new users of non-formulary PDE5s (no use of PDE5s in last 180 days)			21 Oct 09	28 Dec 09 (60 days)
Nov 09 (update; original review May 05)	MS-DMDs	**Recommended for non-formulary status Nov 09** ▪ Beta interferon 1-b injection (Extavia)	ECF	**No changes to ECF recommended Nov 09** ▪ interferon beta-1a intramuscular injection (Avonex)	pending approval (original decision 14 Jul 05)	pending approval (60 days)
Nov 09 (update; original review Nov 05; updated Nov 08 & Aug 08)	Antidepressants I	**Recommended for non-formulary status Nov 09** ▪ bupropion HBr (Aplenzin) ▪ milnacipran (Savella) **Recommended to move from non-formulary status to UF Nov 09** ▪ bupropion extended release (Wellbutrin XL)	BCF	**No changes to BCF recommended Nov 09**	pending approval	pending approval
		▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg weekly admin. (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ desvenlafaxine (Pristiq)		Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen & special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	10 Feb 09; original signing date 24 Oct 08 (Pristiq) 19 Jan 06 (original review)	7 Jan 09 (Pristiq) 19 Jul 06 (180 days)
Nov 09 (update; original review Feb 07)	Narcotic Analgesics	**Recommended for non-formulary status Nov 09** ▪ tramadol ER (Ryzolt) ▪ tapendatol (Nucynta)	BCF	**No changes to BCF recommended Nov 09**	pending approval	pending approval

Meeting	Drug Class	Non-Formulary Medications	[illegible]	[illegible]	[illegible]	[illegible]
		▪ tramadol ER (Ultram ER)		▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
May 09 update; reviewed Aug 08; Feb 06 original review)	Overactive Bladder Drugs	**Recommended for non-formulary status Nov 09;** ▪ oxybutynin topical gel Gelnique)	BCF	**No changes to BCF recommended Nov 09**	pending approval	pending approval
		▪ fesoterodine (Toviaz) (recommended for NF status May 09) ▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)		▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	17 Aug 09 (fesoterodine) 24 Oct 08 (original review)	28 Oct 09(fesoterodine) 4 Feb 09 (original review)
Nov 09	ARB – Renin Angiotensin Antihypertensives	**No changes to NF recommended Nov 09**	BCF	**BCF change recommended Nov 09** ▪ **Delete telmisartan +/- HCTZ (Micardis, Micardis HCT) from BCF**	pending approval	pending approval
Nov 09	ARB/CCB/diuretic Renin Angiotensin Antihypertensives	**No changes to NF recommended Nov 09**		**No changes to BCF recommended Nov 09; valsartan/amlodipine/HCTZ (Exforge HCT) recommended for UF**	pending approval	pending approval

Meeting	Class Class	Non-Formulary Recommendation	BCF/ ECF	BCF/ECF Recommendation	Implementation Date for Non-Formulary Recommendation	Implementation Date for BCF/ECF Recommendation
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Misc. anti-hypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	To remain NF ARB/CCB combos ▪ olmesartan/amlodipine (Azor) – rec NF Jun 08 ▪ valsartan amlodipine (Exforge) ACE inhibitors ▪ Moexipril +/- HCTZ (Univasc; Uniretic) ▪ perindopril (Aceon) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) (D/C'd from market) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan+/- HCTZ (Avapro, Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- (Diovan; Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel, generics) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ARB/CCB combos ▪27 Aug 08 (Azor) ▪13 Feb 08 (Exforge) ▪ACE inhibitors ▪10 Feb 09 (Ramipril removed from NF and moved to UF at Nov 08 mtg) ▪13 Oct 05 ACE/CCB combos ▪26 Apr 06 ▪ARBs ▪24 July 07	ARB/CCB combos Revised implementation date: 26 Nov 08 Azor (60 days) ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07 ▪ 16 Apr 08
Aug 09 (update; original review Nov 2007)	Targeted Immunomodulatory Biologics	Recommended for non-formulary status Aug 09; no change to non-formulary status from Nov 07 ▪ golimumab injection (Simponi) ▪ certolizumab injection (Cimzia)	ECF	No changes to ECF recommendation Nov 07	21 Oct 09	28 Dec 09 (60 days)
		▪ etanercept injection (Enbrel) ▪ anakinra injection (Kineret)	ECF	▪ adalimumab injection (Humira)	13 Feb 08	18 Jun 08 (120 days)
Aug 09 (update; updated Nov 07; original review Aug 05)	Alpha Blockers for BPH	Recommended for non-formulary status Aug 09; no change to non-formulary status from Nov 07 or Aug 05 ▪ silodosin (Rapaflo)	BCF	No changes to BCF recommendation Nov 07	21 Oct 09	28 Dec 09 (60 days)
		▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Aug 09 (update; updated Nov 07; original review Nov 06)	ADHD / Narcolepsy Agents	No change to non-formulary status from Aug 05 or Nov 07	BCF	No changes to BCF recommendation from Aug 05	21 Oct 09	28 Dec 09
		Recommended for non-formulary status Nov 07 ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
May 09 (update; reviewed Jun 08; original review May 07)	Antilipidemic Agents-II	Recommended for non-formulary status May 09; no change to non-formulary status in Jun 08 ▪ fenofibrate acid (Trilipix)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		No changes to NF recommended Jun 08	BCF	Recommended for addition to BCF Jun 08 ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
May 09 (update; reviewed Nov 08) update to include nasal	Nasal Allergy Drugs	Recommended for non-formulary status May 09; no change to non-formulary status in Nov 08 ▪ azelastine with sucralose (Astepro)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
antihistamines ; nasal steroids reviewed Nov 05 & Aug 07 for Veramyst)		• olopatadine (Patanase) • ciclesonide (Omnaris) • fluticasone furoate (Veramyst) • beclomethasone (Beconase AQ) • budesonide (Rhinocort Aqua) • triamcinolone (Nasacort AQ)	BCF	• Fluticasone propionate (generic Flonase) • Azelastine (Astelin)	10 Feb 09	8 Apr 09 (60 days)
May 09 (update; reviewed May 07& Feb 05)	Proton Pump Inhibitors	Recommended for non-formulary status May 09 no change to non-formulary status in May 07 • Dexlansoprazole (Kapidex)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		• lansoprazole (Prevacid) • omeprazole/sodium bicarbonate (Zegerid) • pantoprazole (Protonix) • rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	• generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) • esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 09 (update; reviewed May 06)	Antiemetics	Recommended for non-formulary status May 09; no change to non-formulary status • granisetron transdermal system (Sancuso)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		• dolasetron (Anzemet)	BCF	• promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 09	Inhaled Corticosteroids	• Beclomethasone HFA MDI (Qvar) • Budesonide MFA MDI (Pulmicort Flexhaler) • Ciclesonide HFA MDI (Alvesco) • Flunisolide CFC MDI (Aerobid, Aerobid M) • Triamcinolone CFC MDI (Azmacort)	BCF	• Fluticasone DPI (Flovent Diskus) • Fluticasone HFA MDA (Flovent HFA) • Mometasone DPI (Asmanex Twisthaler)	12 May 2009	16 Sep 09 (120 days)
Feb 09	Long-Acting Beta Agonists	• formoterol inhalation solution (Perforomist)	BCF	• Salmeterol DPI (Serevent Diskus)	12 May 2009	16 Sep 09 (120 days)

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Feb 09	Inhaled Corticosteroids / Long-Acting Beta Agonist Combinations	(No ICS/LABA combinations recommended for NF placement Feb 09)	BCF	• Fluticasone/salmeterol DPI (Advair Diskus) • Fluticasone/salmeterol HFA MDI (Advair HFA)	12 May 2009	16 Sep 09 (120 days)
Nov 08	Short-Acting Beta Agonists	• albuterol chlorofluorocarbon (CFC) metered dose inhaler (MDI) (no longer manufactured) • metaproterenol (Alupent) CFC MDI (no longer marketed) • metaproterenol inhalation solution • pirbuterol (Maxair) MDI	BCF	• Ventolin HFA (albuterol hydrofluoroalkane (HFA) MDI • Albuterol inhalation solution; Note – does not include the following: Accuneb 0.021% [0.63 mg/mL] Accuneb 0.042% [1.25 mg/3mL] Albuterol 0.5% [2.5 mg/0.5 mL in 0.5 unit dose vial]	10 Feb 09	8 Apr 09 (60 days)
Oct 08 (interim teleconference meeting) & Jun 08	Triptans	• almotriptan (Axert) • frovatriptan (Frova) • naratriptan (Amerge)	BCF	• rizatriptan (Maxalt), immediate upon signing of the minutes • sumatriptan oral and one injectable formulation, when multi-source generics are available	24 Oct 08;; original signing date: 27 Aug 08	26 Nov 08 (90 days)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	• OneTouch Ultra 2 strips (for OneTouch Ultra 2, Ultra Mini, and Ultra Smart meters) • TrueTrack strips (for TrueTrack meter) • Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) • Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) • Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check • Plus all other store/private label brand strips not included on the UF (see BCF/ECF column)	BCF	**Basic Core Formulary SMBGS test strips** • Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** • Accu-chek Aviva (for Accu-chek Aviva meter) • Ascensia Contour (for Ascensia Contour meter) • Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	24 Oct 08	17 Mar 09 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF ECF Class	BCF/ECF Medications	Decision Date [illegible]	Effective Date of Non-formulary Medications [illegible]
Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	Recommended for non-formulary status Aug 08 ▪ nisoldipine geomatrix (Sular geomatrix)	BCF	No changes to BCF recommended Aug 08	24 Oct 08	7 Jan 09 (60 days)
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR, ER (Dynacirc; Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER HS dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	Recommended for non-formulary status Jun 08 ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	Recommended for non-formulary status Jun 08 ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)

[illegible]	[illegible] Class	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
		To remain NF • desloratadine (Clarinex) • desloratadine/pseudoephedrine (Clarinex D)		• MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	Recommended for non-formulary status Jun 08 • Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF • zileuton (Zyflo)		Currently BCF • montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Nov 07 (update, original review May 06)	Contraceptives	Recommended for non-formulary status Nov 07 • EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF • EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) • EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) • EE 50 mcg / norethindrone 1 mg (Ovcon 50) • EE 20/30/35 mcg / noreth. 1 mg (Estrostep Fe)		Currently on the BCF • EE 20 mcg / 3 mg drospirenone (Yaz) • EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) • EE 30 mcg / 3 mg drospirenone (Yasmin) • EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) • EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) • EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) • EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) • EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) • 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		• EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) • EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	• somatropin (Genotropin, Genotropin Miniquick) • somatropin (Humatrope) • somatropin (Omnitrope) • somatropin (Saizen)	ECF	• somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)

[illegible]	Drug Class	[illegible]	BCF or ECF	[illegible]	[illegible]	[illegible]
May 07	5-Alpha Reductase Inhibitors	• dutasteride (Avodart)	BCF	• finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	• zolpidem ER (Ambien CR) • zaleplon (Sonata) • ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	• zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	• selegiline transdermal patch (Emsam)	ECF	• phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	• tramadol ER (Ultram ER)	BCF	• morphine sulfate IR 15 mg, 30 mg • morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg • oxycodone/APAP 5/325 mg • hydrocodone/APAP 5/500 mg • codeine/APAP 30/300 mg • codeine/APAP elixir 12/120 mg/5 mL • tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	• travoprost (Travatan, Travatan Z) • timolol maleate for once daily dosing (Istalol) • timolol hemihydrate (Betimol) • brinzolamide (Azopt)	BCF	• latanoprost (Xalatan) • brimonidine (Alphagan P); excludes 0.1% • timolol maleate • timolol maleate gel-forming solution • pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	• temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	Recommended for non-formulary status Nov 06: 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)
		• econazole • ciclopirox • oxiconazole (Oxistat) • sertaconazole (Ertaczo) • sulconazole (Exelderm)		• nystatin • clotrimazole	17 Jan 07	18 Mar 07 (60 days)

[illegible]	[illegible] Class	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Aug 06	H2 Antagonists / GI protectants	-	BCF	• ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	• rosuvastatin (Crestor) • atorvastatin / amlodipine (Caduet)	BCF	• simvastatin (Zocor) • pravastatin • simvastatin / ezetimibe (Vytorin) • niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
Feb 06	GABA-analogs	• pregabalin (Lyrica)	BCF	• gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	• tacrine (Cognex)	ECF	• donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	• azithromycin 2 gm (Zmax) • telithromycin (Ketek)	BCF	• azithromycin (Z-Pak) • erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
CFC = chlorofluorocarbon; ER = extended release; HFA = hydrofluoroalkane; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle;
AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; ED = erectile dysfunction; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HBr = hydrobromide; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MDIs = metered dose inhalers; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; NADs = Nasal Allergy Drugs; OABs = Overactive Bladder Medications; PAH = pulmonary arterial hypertension; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SABAs = Short-Acting Beta Agonists; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones
*The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix F — Table of Abbreviations

6MWD	6-minute walking distance
ACE	angiotensin converting enzyme
AD-1	antidepressant-1 drug class
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CCB	calcium channel blocker
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
DHP	dihydropyridine CCB
DoD	Department of Defense
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HBr	hydrobromide
HCl	hydrochloride
HCTZ	hydrochlorothiazide
IR	immediate release
M2	MHS Data mart
MHS	Military Health System
MN	medical necessity
MS-DMDs	multiple sclerosis disease modulating drugs class
MTF	Military Treatment Facility
NDAA	National Defense Authorization Act
OAB	overactive bladder drug class
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAH	pulmonary arterial hypertension
PDE-5	phosphodiesterase-type 5 inhibitor drug class
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
POS	point of service
QL	quantity limit
RAAs	renin-angiotensin antihypertensive drug class
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SR	sustained release
TCA	tricyclic antidepressant
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPHARM	TRICARE Pharmacy Benefit Program
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
August 2009

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on August 12, 2009 and August 13, 2009 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is found in Appendix A.

A. Review Minutes of Last Meetings

1. Revisions to the minutes — Revisions to the May 2009 minutes will be reviewed at the November 2009 DoD P&T Committee meeting.
2. Approval of May minutes — The minutes from the DoD P&T Committee meeting held May 13, 2009 are still undergoing review.

III. REVIEW OF RECENTLY FDA-APPROVED AGENTS

A. Targeted Immunomodulatory Biologics (TIBs) — Golimumab injection (Simponi)

Relative Clinical Effectiveness — Golimumab injection (Simponi) is a humanized monoclonal antibody that inhibits biological activity of tumor necrosis factor alpha (TNFα). Golimumab injection is classified in the Targeted Immunomodulatory Biologic (TIB) drug class, which was reviewed for Uniform Formulary (UF) placement in November 2007.

1. *Background* — The clinical evaluation for golimumab included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). Golimumab is administered subcutaneously (SQ) once a month. It is FDA-approved for the treatment of moderate to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX), moderate to severely active psoriatic arthritis (PsA) alone or in combination with MTX, and active ankylosing spondylitis (AS) in adults. The other injectable TNFα inhibitors with multiple FDA-approved indications for use include adalimumab (Humira), etanercept (Enbrel), and certolizumab (Cimzia).

2. *Efficacy and Safety* — Golimumab was superior to placebo in the treatment of RA, PsA, and AS in the pivotal phase III trials used to obtain FDA approval. There are no direct comparative clinical trials between golimumab and other TNFα inhibitors. There is insufficient evidence to

determine whether treatment with golimumab would result in greater clinical response than other TNF inhibitors. The safety profile of golimumab reflects that of the other anti-TNF agents currently on the market.

3. *Other Factors* — The Pharmacy Outcomes Research Team (PORT) reported results of an analysis evaluating patterns of use of adalimumab (Humira) and etanercept (Enbrel) among 6,257 new Military Health System (MHS) users. Overall, persistence at ~3 years ranged from 35% to 57%. Switching between the two drugs occurred relatively rarely, as 15% (938/6,257) of patients switched once, and 2% subsequently switched back to the original agent. Most patients who were on MTX prior to starting adalimumab or etanercept continued to receive MTX (2,327/3,027 = 77%), but it was relatively uncommon for MTX to be started with or after the TIB for patients who were MTX-naive (642/3,230 = 20%). Overall, about 5% of patients were considered to be potentially "dissatisfied" with the available multi-indication TIBs, based on switching between etanercept and adalimumab, followed by discontinuation. Based on these data, the P&T Committee agreed that clinical coverage in the TIB class appears adequate overall as relatively few patients (17%) switch between the two multi-use TIBs in the first ~3 years of treatment, and only about 5% discontinue treatment after trying both.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) that although golimumab injection (Simponi) requires less frequent administration than the other multi-indication TIBs, it did not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other TIBs currently included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the multi-indication agents in the TIB class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). A cost minimization analysis (CMA) was used to evaluate the cost-effectiveness of golimumab.

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 0 abstained, 1 absent) golimumab injection (Simponi) was not cost effective compared to

other agents currently on the UF. Results of the CMA confirmed that adalimumab remains the most cost-effective TIB agent available on the UF.

a) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 0 opposed, 0 abstained, 1 absent) golimumab injection (Simponi) be designated non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the determination that adalimumab (Humira) remains the most cost effective multi-indication TIB on the UF compared to golimumab (Simponi).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

b) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** — Based on the clinical evaluation of golimumab injection (Simponi) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (12 for, 0 opposed, 0 abstained, 1 absent) MN criteria for golimumab injection (Simponi). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

c) ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee voted (11 for, 0 opposed, 1 abstained, 1 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

d) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** — Currently PA requirements apply to etanercept (Enbrel), adalimumab (Humira) and the other TIBs. The P&T Committee agreed that the following PA criteria should apply to golimumab injection, consistent with the FDA-approved labeling and PA requirements for the other TIBs.

(1) Coverage would be approved for the treatment of adult patients with moderate to severely active RA in combination with MTX, moderate to severely active PsA alone or in combination with MTX, and active AS in adults.

(2) Coverage would not be provided for concomitant use with abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), or rituximab (Rituxan).

The P&T Committee voted (12 for, 0 opposed, 0 abstained, 1 absent) to recommend the PA criteria outlined above. See Appendix C for full PA criteria.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

e) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) IMPLEMENTATION PLAN*** — The P&T Committee voted (11 for, 0 opposed, 1 abstained, 1 absent) to recommend the effective date for the golimumab injection (Simponi) be timed to coincide with that established for the UF decision for golimumab injection (Simponi).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

f) ***COMMITTEE ACTION: QUANTITY LIMITS*** — Quantity limits (QLs) or days supply limits currently apply to etanercept (Enbrel) and adalimumab (Humira) as outlined in Appendix C, and the other TIBs. The P&T Committee voted (12 for, 0 opposed, 0 abstained, 1 absent) to recommend QLs for golimumab injection (Simponi) consistent with FDA-approved labeling and the requirements for the other TIBs. See Appendix C for full recommended QLs.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Targeted Immunomodulatory Biologics (TIBs) — Certolizumab Injection (Cimzia)

Relative Clinical Effectiveness — Certolizumab injection (Cimzia) is a TNFα inhibitor that is conjugated to polyethylene glycol to increase the duration of action. Certolizumab injection is classified in the Targeted Immunomodulatory Biologic (TIB) drug class that was reviewed for Uniform Formulary (UF) placement in November 2007.

1. *Background* — The certolizumab (Cimzia) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). Certolizumab (Cimzia) is available as a lyophilized powder for reconstitution and a solution for SQ injection. It is dosed once monthly for Crohn's disease and every two weeks (with the option of once monthly dosing) for RA. Certolizumab (Cimzia) is FDA-approved for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderate to severely active disease refractory to conventional therapy. It is also approved for the treatment of moderate to severely active RA in adults.

2. *Efficacy and Safety* — There are no direct comparative clinical trials between certolizumab and other TNF inhibitors. Phase III trials demonstrated that certolizumab (Cimzia) was more effective than placebo in achieving and maintaining clinical response in Crohn's disease and RA, and was also more effective than placebo in delaying the progression of structural damage in patients with active RA. There is insufficient evidence to determine whether certolizumab would result in greater response than other anti-TNF agents, and pegylation did not appear to confer added benefits in efficacy or toxicity profile. In general, the safety profile of certolizumab is similar to that of the other TNF inhibitors.

3. *Other Factors* — Based on the Pharmacy Outcomes Research Team (PORT) analysis previously discussed, the P&T Committee agreed that clinical coverage in the TIB class appears adequate overall as relatively few patients (17%) switch between the two multi-use TIBs in the first ~3 years of treatment, and only about 5% discontinue treatment after trying both.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (12 for, 0 opposed, 0 abstained, 1 absent) that although certolizumab injection (Cimzia) has the potential for less frequent administration than adalimumab (Humira) and etanercept (Enbrel), it did not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other TIBs currently included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the multi-indication agents in the TIBs class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). A cost minimization analysis (CMA) was used to evaluate the cost-effectiveness of certolizumab (Cimzia).

Relative Cost-Effectiveness Conclusion — The P&T Committee concluded (12 for, 0 opposed, 0 abstained, 1 absent) certolizumab injection (Cimzia) is not cost effective relative to other formulary TIBs agents.

a) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 0 opposed, 0 abstained, 1 absent) that certolizumab

injection (Cimzia) be designated non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the determination that adalimumab (Humira) remains the most cost effective multi-indication TIB on the UF compared to certolizumab injection (Cimzia).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

b) ***COMMITTEE ACTION: MN CRITERIA*** — Based on the clinical evaluation of certolizumab (Cimzia) and the conditions for establishing MN of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (12 for, 0 opposed, 0 abstained, 1 absent) MN criteria for certolizumab injection (Cimzia). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

c) ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee voted (12 for, 0 opposed, 0 abstained, 1 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

d) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** — Currently PA requirements apply to etanercept (Enbrel), adalimumab (Humira) and the other TIBs. The P&T Committee agreed that the following PA criteria should apply to certolizumab injection (Cimzia), consistent with the FDA-approved labeling and PA requirements for the other TIBs.

(1) Coverage would be approved for reducing signs and symptoms of Crohn's disease, maintaining clinical response in adult patients with moderate to severely active disease refractory to conventional therapy, and for the treatment of moderate to severely active RA in adults.

(2) Coverage would not be provided for concomitant use with abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), or rituximab (Rituxan).

The P&T Committee voted (11 for, 0 opposed, 1 abstained, 1 absent) to recommend the PA criteria outlined above. See Appendix C for full PA criteria.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

e) ***COMMITTEE ACTION: PA IMPLEMENTATION PLAN*** — The P&T Committee voted (12 for, 0 opposed, 0 abstained, 1 absent) to recommend the effective date for the certolizumab injection (Cimzia) be timed to coincide with that established for the UF decision for certolizumab Cimzia).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

f) ***COMMITTEE ACTION: QUANTITY LIMITS*** —The P&T Committee voted (12 for, 0 opposed, 0 abstained, 1 absent) to recommend QLs for certolizumab injection (Cimzia) consistent with FDA-approved labeling and the requirements for the other TIBs. See Appendix C for full recommended QLs.

ActingDirector, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

C. Alpha Blockers for Benign Prostatic Hyperplasia (BPH) — Silodosin capsules (Rapaflo)

Relative Clinical Effectiveness — Silodosin (Rapaflo) is an alpha blocker FDA-approved for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The alpha blockers for BPH were last reviewed for UF placement in November 2007. Silodosin (Rapaflo) is similar to tamsulosin (Flomax); it is a highly selective antagonist of α1A-adrenoceptors (α1A-AR) in the prostate. Alfuzosin (Uroxatral) is the third uroselective alpha blocker for BPH in the class.

The silodosin capsules (Rapaflo) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no direct comparative clinical trials between silodosin and the other alpha blockers for BPH, and no trials are available that evaluate outcomes other than changes in signs and symptoms of BPH. The clinical trials used to obtain FDA approval reported silodosin is effective at reducing International Prostate Symptom Score (IPSS) (which signifies reduction in symptoms) and increasing maximum urinary flow rate (Qmax) in patients with BPH. Improvements in the IPSS score and Qmax are comparable to the changes seen with the other alpha blockers. The safety profile of silodosin (Rapaflo) appears to be comparable to other uroselective agents.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) silodosin capsules (Rapaflo) do not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other alpha blockers for BPH currently included on the UF.

Relative Cost-Effectiveness — The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the Alpha Blocker class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of silodosin capsules (Rapaflo) relative to other UF alpha blocking agents. Results from the CMA showed the projected weighted average cost per day for silodosin (Rapaflo) is higher than alfuzosin (Uroxatral). The CMA also revealed the projected weighted average cost per day for silodosin (Rapaflo) is lower than the non-formulary alpha blocking agent, tamsulosin (Flomax). Alfuzosin (Uroxatral) remains the most cost effective alpha blocking agents on the UF.

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 0 absent) that silodosin capsules (Rapaflo) are not cost effective relative to other alpha blockers for BPH included on the UF. Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

1. Results of the CMA revealed that silodosin (Rapaflo) was more cost effective than tamsulosin (Flomax) and was not cost-effective compared to alfuzosin (Uroxatral).

2. Results of the CMA confirmed that alfuzosin (Uroxatral) remains the most cost-effective alpha blocking agent available on the UF.

a) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) that silodosin capsules (Rapaflo) be designated non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the

determination that alfuzosin (Uroxatral) remains the most cost effective uroselective alpha blocker for BPH on the UF compared to silodosin capsules (Rapaflo).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

b) ***COMMITTEE ACTION: MN CRITERIA*** — Based on the clinical evaluation of silodosin and the conditions for establishing MN of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for silodosin capsules (Rapaflo) when use of formulary alternatives is contraindicated, when the patient has experienced significant adverse effects from formulary alternatives, when formulary agents have resulted in therapeutic failure, or when the patient requires a drug that can be crushed or sprinkled on food. (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

c) ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

d) ***COMMITTEE ACTION: PA CRITERIA*** —An automated prior authorization (APR) or *step therapy* is currently in effect and requires use of UF alfuzosin (Uroxatral) before other non-formulary alpha blockers for BPH, unless there is therapeutic failure, intolerance, or hypersensitivity. The Committee agreed that the following PA criteria should apply to silodosin capsules (Rapaflo). Coverage would be approved if the patient met any of the following criteria:

(1) Automated PA criteria:

(a) The patient has received a prescription for either silodosin (Rapaflo) or alfuzosin (Uroxatral) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) PA criteria if automated criteria are not met:

(a) The patient has tried alfuzosin (Uroxatral) and had an inadequate response or was unable to tolerate treatment due to adverse effects.

(b) Treatment with alfuzosin (Uroxatral) is contraindicated.

(c) The patient requires an alpha blocker that can be crushed and sprinkled on food.

e) ***COMMITTEE ACTION:*** The P&T Committee voted (12 for, 0 opposed, 1 abstained, 0 absent) to recommend the PA criteria outlined above.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

f) ***COMMITTEE ACTION: PA IMPLEMENTATION PLAN*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend the effective date for the silodosin (Rapaflo) PA be timed to coincide with that established for the UF decision for silodosin.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

D. Narcolepsy/Attention Deficit Hyperactivity Disorder (ADHD) — Armodafinil tablets (Nuvigil)

Relative Clinical Effectiveness — Armodafinil (Nuvigil) is a non-amphetamine wakefulness promoting agent. It is the single R-enantiomer of modafinil (Provigil), which is a racemic mixture. The R-enantiomer has been shown to have a longer half-life than its S-counterpart; however, the half-lives of armodafinil and modafinil are similar. The subclass of narcolepsy agents was last reviewed in November 2006 as part of the ADHD and narcolepsy drug class. The other narcolepsy agents on the uniform formulary are modafinil (Provigil) and sodium oxybate.

Armodafinil (Nuvigil) is FDA-approved for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. These are the same FDA indications as the current UF agent modafinil (Provigil). Generic formulations of modafinil (Provigil) are expected in mid-2010.

The armodafinil (Nuvigil) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no head-to-head trials comparing armodafinil (Nuvigil) to modafinil (Provigil) and there is no conclusive data to support longer-lasting effects of armodafinil (Nuvigil) as compared to modafinil (Provigil). After review of the clinical literature, armodafinil (Nuvigil) does not have compelling clinical advantages over existing narcolepsy agents on the UF. There is currently insufficient data to conclude that armodafinil (Nuvigil) offers improved efficacy, safety, or tolerability compared to modafinil (Provigil).

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (12 for, 0 opposed, 1 abstained, 0 absent) there is currently insufficient data to conclude that armodafinil (Nuvigil) offers improved efficacy, safety, or tolerability compared to the UF product modafinil (Provigil).

Relative Cost-Effectiveness — The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the Narcolepsy/ADHD class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). A cost minimization analysis (CMA) was used to evaluate the cost-effectiveness of armodafinil tablets (Nuvigil).

Relative Cost-Effectiveness Conclusion — The P&T Committee, based upon its collective professional judgment, voted (10 for, 2 opposed, 0 abstained, 1 absent) that armodafinil tablets (Nuvigil) are cost effective relative to modafinil (Provigil). Results of the CMA revealed that armodafinil was more cost effective than modafinil, the only UF agent.

a) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 0 opposed, 1 abstained, 0 absent) that armodafinil tablets (Nuvigil) be designated formulary on the UF.

Acting Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

b) ***COMMITTEE ACTION: BCF RECOMMENDATION*** — Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 0 abstained, and 0 absent) to recommend armodafinil (Nuvigil) not be added to the BCF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

c) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** — Taking into consideration the clinical review, the P&T Committee recommended the following PA criteria should apply to armodafinil (Nuvigil). Coverage would be approved if a patient met any of the following criteria and would expire in 1 year:

(1) Narcolepsy associated with persistent and excessive daytime sleepiness as diagnosed by polysomnogram or mean sleep latency time (MSLT) objective testing;

(2) Obstructive sleep apnea associated with persistent and excessive daytime sleepiness (CPAP treatment adequately titrated and patient is compliant with treatment); and

(3) Nightshift worker with diagnosis of shift-work sleep disorder associated with excessive sleepiness.

d) ***COMMITTEE ACTION:*** The P&T Committee voted (12 for, 1 opposed, 0 abstained, 0 absent) to recommend PA criteria for armodafinil (Nuvigil) as outlined above.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

e) ***COMMITTEE ACTION: PA IMPLEMENTATION PLAN*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Allen P. Rubley

IV. UNIFORM FORMULARY DRUG CLASS REVIEWS

A. Phosphodiesterase-Type 5 (PDE-5) Inhibitors

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the Phosphodiesterase Type-5 (PDE-5) inhibitors for the treatment of erectile dysfunction (ED). The drug class was previously reviewed for UF placement in May 2005. The class is comprised of two subclasses, PDE-5 inhibitors for ED; sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra); and those for pulmonary artery hypertension (PAH): sildenafil (Revatio) and tadalafil (Adcirca). The PDE-5 inhibitors for PAH will be evaluated at a future P&T Committee meeting.

Information regarding the safety, effectiveness, and clinical outcomes of the PDE-5s for ED subclass was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

MHS expenditures for the PDE-5 inhibitors exceeded $54M in FY 2008 (MTF: $9.75M; TRICARE Retail Network [TRRx]: $36M; and TRICARE Mail Order Pharmacy [TMOP]: $9M). At the MTFs, vardenafil (Levitra) designated an Extended Core Formulary agent, is the highest utilized PDE-5 inhibitor, while sildenafil (Viagra) is the highest utilized drug at the TRRx.

Relative Clinical Effectiveness Conclusion — The P&T Committee recommended the following clinical effectiveness conclusions regarding PDE-5 inhibitors:

1. With regard to efficacy, the following conclusions were made:
   a) ED: Sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) are FDA-approved for the treatment of ED. There are no head-to-head trials comparing the three PDE-5 inhibitors.

      (1) There is insufficient evidence to conclude that there are clinically relevant differences in efficacy of PDE-5 inhibitors for ED. Although all PDE-5s are clinically superior to placebo, the variability in study design, demographics, and outcome measures

precludes the ability to designate one PDE-5 as clinically superior.

(2) Based on meta-analyses by Agency for Healthcare Research and Quality, the Cochrane reviewers, and BioMed Central, indirect comparisons suggest that there are similar improvements between the three PDE-5 inhibitors in endpoints or International Index of Erectile Function (IIEF) domain change score for erectile function, the percentage of patients responding "yes" on the Global Assessment Questionnaire, question one, the percentage of patients with improved erections, and numbers needed to treat for these endpoints.

(3) One Cochrane analysis found that PDE-5 inhibitors improve erections in diabetic patients.

(4) There is insufficient evidence to conclude that daily therapy for ED is superior to on-demand therapy.

b) PAH: Sildenafil (under the trade name Revatio), and tadalafil (under the trade name Adcirca) both have FDA-approved indications for treating PAH.

c) Preservation/restoration of erectile function after prostatectomy: The P&T Committee agreed that the evidence, based on positive results from published clinical trials, was supportable for daily use of the PDE-5 inhibitors for this off-label indication.

d) Raynaud's Phenomenon: Although results are conflicting and larger, longer-term trials are needed, benefits have been shown with daily use of PDE-5 inhibitors in terms of improvements in digital blood flow in patients with Raynaud's disease. The P&T Committee agreed that this was a supportable off-label use.

e) Other off-label uses: The P&T Committee agreed that the current published literature is insufficient to support use of PDE-5 inhibitors for female sexual dysfunction, hypertension, esophageal motility disorders, ocular blood flow disorders, Eisenmenger's Syndrome, premature ejaculation, recurrent ischemic priapism, and lower urinary tract symptoms due to benign prostatic hypertrophy (BPH).

2. With regards to safety and tolerability, the P&T Committee agreed that there is insufficient evidence to conclude that there are clinically relevant differences in safety between PDE-5s for ED. The product labeling for the three drugs is similar with regard to contraindications, precautions, and warnings. The causal relationship of PDE-5 inhibitors to non-arteritic anterior ischemic optic neuropathy or hearing loss are uncertain at this time.

3. With regards to other factors between the PDE-5s, results from a questionnaire sent to a convenience sample of MTF providers found that about 34% of the respondents ranked sildenafil (Viagra) as their first choice of PDE-5 for treating ED; over 25% stated no preference; 22% ranked tadalafil (Cialis) as their first choice; and 19% ranked vardenafil (Levitra) as their first choice. Approximately 82% of providers felt that on-demand therapy was sufficient to meet the needs of their patients, and approximately 73% of respondents did not feel that it was important to have a PDE-5 inhibitor approved for daily therapy available on the UF. About half of respondents (49%) indicated that the current quantity limit of PDE-5 for ED (6 tablets per month) was appropriate. However, for providers who felt the quantity limit should be increased, the median and mode response was 10 tablets/30 days. Currently, PDE-5 inhibitors do not require prior authorization (PA) for organic ED in men over 50 years old. Responses showed a majority (63%) of providers felt that the current age limit is not appropriate. Over half of respondents (55%) indicated a new automated prior authorization age limit of 40 years was appropriate.

   (1) ***COMMITTEE ACTION:*** The P&T Committee voted (11 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

Relative Cost Effectiveness — In considering the relative cost-effectiveness of pharmaceutical agents in the PDE-5 for ED subclass, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the subclass. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) and budget impact analysis (BIA) were used to evaluate the cost effectiveness of the PDE-5 agents.

Relative Cost Effectiveness Conclusion — Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) the following. Results from the CMA of PDE-5s for ED agents revealed that vardenafil (Levitra) was the most cost effective PDE-5 agent. The potential impact of scenarios with selected PDE-5 was evaluated with a BIA. Results from the BIA of PDE-5s for ED revealed that placing vardenafil (Levitra) on the UF in conjunction with a PA requiring a trial of Levitra for new patients was the most cost effective scenario overall. Lowering the age limit for automatic PA approval of the treatment of typical organic erectile dysfunction in

males from 50 to 40 years old would add about 3.7% to the cost of each scenario reviewed. Increasing the quantity limits would increase the cost.

(2) ***COMMITTEE ACTION:*** The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to accept the cost effectiveness conclusions stated above.

(3) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent):

(a) Vardenafil (Levitra 2.5 mg, 5 mg, 10 mg, and 20 mg) be classified as formulary on the UF.

(b) Sildenafil (Viagra 25 mg, 50 mg, and 100 mg) and tadalafil (Cialis 2.5 mg, 5 mg, 10 mg, and 20 mg) be designated as nonformulary under the UF, based on cost effectiveness.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

(4) ***COMMITTEE ACTION: MN CRITERIA*** — Based on the clinical evaluation of sildenafil (Viagra) and tadalafil (Cialis) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for Viagra and Cialis. (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

(5) ***COMMITTEE ACTION: UNIFORM FORMULARY (UF) IMPLEMENTATION PERIOD*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

(6) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) CRITERIA*** — The P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent, with the exceptions noted below) the following PA criteria should apply to PDE-5 inhibitors other than vardenafil (Levitra). Coverage would be approved if a patient met any of the following criteria, and would expire in one year:

(a) Automated PA criteria:
- (i) The patient has received a prescription for sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
- (ii) The patient is a male, aged 40 years or older (12 for, 1 opposed, 0 abstained, 0 absent)

(b) PA if automated criteria are not met:
- (i) The patient has tried vardenafil (Levitra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.
- (ii) Treatment with vardenafil (Levitra) is contraindicated.
- (iii) Sildenafil (Viagra or Revatio) or tadalafil (Cialis or Adcirca) is for treatment of Pulmonary Artery Hypertension (PAH).

(iv) Use is for preservation/restoration of erectile function after prostatectomy.

(v) Use is for Raynaud's Phenomenon (12 for, 1 opposed, 0 abstained, 0 absent).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

(7) ***COMMITTEE ACTION: PRIOR AUTHORIZATION (PA) IMPLEMENTATION PLAN*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend an implementation plan for the PA be timed to coincide with that established for the UF decision for sildenafil and tadalafil.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

(8) ***COMMITTEE ACTION: QUANTITY LIMITS*** — The P&T Committee considered the QL for the treatment of ED as well as QL for other indications. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 0 abstained, and 0 absent) to recommend maintaining the existing QL for the treatment of typical organic ED of a collective 18 tablets/90 days in the TMOP and 6 tablets/30 days in the TRRx and to accommodate daily therapy for PAH, preservation or restoration of erectile function after prostatectomy, and Raynaud's Phenomenon by setting QLs at a 90-day supply in the TMOP and a 30-day supply in the TRRx.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

(9) ***COMMITTEE ACTION: BASIC CORE FORMULARY DECISION*** — The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend that vardenafil (Levitra) 2.5 mg, 5 mg, 10 mg, and 20 mg tablets be designated as BCF immediately on signing of the August 2009 P&T Committee minutes by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

V. UTILIZATION MANAGEMENT — PRIOR AUTHORIZATIONS (PA) / Quantity Limits (QL) / MEDICAL NECESSITY (MN)

A. Modafinil (Provigil) — Prior Authorization. New data published since the original Narcolepsy drug class review in November 2006 was evaluated to determine if the modafinil (Provigil) PA required updating. The P&T Committee agreed the evidence for using modafinil (Provigil) for sleepiness associated with Parkinson's disease was not supportable. Recommendations for treating fatigue associated with traumatic brain injury (TBI) were mentioned in a recent VA/DoD guideline, and this usage was deemed supportable by the P&T Committee. In the one published, double-blinded, randomized, controlled trial conducted in patients with varying severities of TBI, there was no difference in fatigue or sleepiness associated with TBI between the modafinil groups and placebo. The VA/DoD guidelines pertaining to mild TBI state there is no evidence regarding use of medications in patients recovering from mild TBI and recommend avoiding medications; however, modafinil would be a first-line agent for fatigue based on expert opinion, if medications were initiated. The P&T Committee also recommended updating the criteria used for objectively diagnosing narcolepsy via polysomnogram or mean sleep latency testing (MSLT).

1. ***COMMITTEE ACTION — PA CRITERIA:*** The Committee voted (11 for, 2 opposed, 0 abstained, 0 absent) the following PA criteria should apply to modafinil (Provigil). Coverage would be approved if a patient met any of the following criteria and would expire in 1 year.

a) Narcolepsy associated with persistent and excessive daytime sleepiness as diagnosed by polysomnogram or MSLT objective testing;

b) Obstructive sleep apnea associated with persistent and excessive daytime sleepiness AND continuous positive airway pressure (CPAP) treatment adequately titrated and patient compliant with treatment;

c) Nightshift worker with diagnosis of shift work sleep disorder associated with excessive sleepiness;

d) Multiple sclerosis with excessive fatigue and secondary causes have been addressed;

e) Myotonic dystrophy associated with excessive fatigue;

f) A diagnosis of depression AND primary antidepressant therapy (defined as 4–6 week trial of at least one antidepressant agent) has failed AND the use of other stimulant augmentation (such as methylphenidate products) is contraindicated due to adverse effects, previous failure, or hypersensitivity;

g) Idiopathic hypersomnia diagnosed by a sleep specialist;

h) Fatigue associated with mild traumatic brain injury.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

2. ***COMMITTEE ACTION — PA IMPLEMENTATION PLAN:*** The Committee voted (12 for, 0 opposed, 1 abstained, 0 absent) to recommend an implementation date effective date of the first Wednesday one week after the minutes are signed. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

B. Tramadol extended release (Ryzolt) — QL: A new extended-release formulation of tramadol extended release (ER) (Ryzolt) has been marketed. Tramadol ER will be reviewed for UF status at an upcoming P&T Committee meeting as a newly-approved drug. QLs are currently in place for both immediate and extended-release tramadol (Ultram, Ultram ER, generics), which are consistent with the product labeling.

1. ***COMMITTEE ACTION — QL:*** The Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend QLs for Ryzolt as outlined in Appendix D.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. QL Updates: In anticipation of the forthcoming TPHARM contract implementation, the P&T Committee updated the quantity limits (QLs) for several drugs: mometasone dry powder inhaler (Asmanex Twisthaler), fluticasone dry powder inhaler (Flovent diskus), fluoxetine for weekly dosing (Prozac weekly), azelastine (Astelin), and azelastine with sucrose nasal inhalers (Astepro), which is consistent with QLs for other drugs in the class, and approved product dosing. See Appendix D.

1. ***COMMITTEE ACTION:*** The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend the QLs for mometasone dry powder inhaler (Asmanex Twisthaler), fluticasone dry powder inhaler (Flovent Diskus), fluoxetine for weekly dosing (Prozac Weekly), azelastine (Astelin) and azelastine with sucrose (Astepro) nasal inhalers, as outlined in Appendix D.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. NATIONAL DEFENSE AUTHORIZATION ACT (NDAA) SECTION 703 — INCLUSION OF TRICARE RETAIL PHARMACY PROGRAM IN FEDERAL PROCUREMENT OF PHARMACEUTICALS UPDATE

The committee reviewed drugs that were not included on a Department of Defense Retail Refund Pricing Agreement; these drugs are not compliant with FY2008 National Defense Authorization Act, Section 703. The law stipulates that if a drug is not compliant with Section 703, these drugs will be designated non-formulary under the Uniform Formulary and will require a pre-authorization prior to use in the retail point of service and medical necessity in military treatment facilities. These non-formulary drugs will remain available in the mail order point of service (POS) without pre-authorization. Pre-authorization will be determined at the November 2009 DoD P&T Committee meeting. Drugs with and without pricing agreements were systematically classified based along therapeutic and pharmacologic lines. The classification system was based on the American Hospital Formulary System Classification and First Data Bank classification. See Appendix E for the full list of affected medications.

A. ***COMMITTEE ACTION — DRUGS RETAINING UF STATUS:*** The P&T Committee voted (11 for, 1 against, 0 abstained, 1 absent) to recommend the drugs listed in Appendix E, Section A to retain formulary status on the Uniform Formulary.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

B. ***COMMITTEE ACTION — DRUGS DESIGNATED OR RETAINED AS NON-FORMULARY:*** The P&T Committee voted (11 for, 1 against, 0 abstained, 1 absent) to recommend the drugs listed in Appendix E, Section B to retain non-formulary status or be designated non-formulary on the Uniform Formulary.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Ellen P. Embrey

C. ***COMMITTEE ACTION — IMPLEMENTATION DATE FOR PRE-AUTHORIZATION:*** The P&T Committee voted (13 for, 0 against, 0 abstained, 0 absent) to recommend the implementation date will not be prior to 1 January 2010 and not later than 180 days after the minutes of this meeting are signed. Formulary status of a drug in these lists will revert back to previous formulary status if Price Agreements are received prior to October 14, 2009.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION — TRANSITION DATE AT THE MTF POS:*** The P&T Committee voted (13 for, 0 against, 0 abstained, 0 absent) to recommend a transition period at the MTF POS as ending no later than 1 January 2011.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

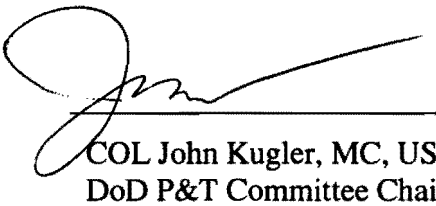
VII. ADJOURNMENT

The meeting adjourned at 1600 hours on August 12, 2009, and at 1300 hours on August 13, 2009. The next meeting will be in November 2009.

Appendix A — Attendance
Appendix B — Table of Medical Necessity Criteria
Appendix C — Table of Prior Authorization and Quantity Limits for the TIBs
Appendix D — Table of Quantity Limits
Appendix E — National Defense Authorization Act (NDAA) Section 703 – Affected Medications
Appendix F — Table of Implementation Status of UF Recommendations/Decisions

Appendix G — Table of Abbreviations

SUBMITTED BY:



COL JAMES CLLZY for

COL John Kugler, MC, USA
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

Ellen P. Embrey
Acting Director

10/21/09
(Date)

Appendix A – Attendance

Voting Members Present	
COL John Kugler, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director DoD Pharmacoeconomic Center (Recorder)
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician, Alternate
COL Peter Bulatao *for Col Carole Labadie, MSC*	Army, Pharmacy Officer, Alternate
CDR Phil Blaine *for CAPT Stephanie Simon, MSC*	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
COL Ted Cieslak, MC	Army, Physician at Large
LTC Bruce Lovins	Army, Family Practice Physician, Alternate
CDR David Tanen, MC	Navy, Physician at Large
Col Everett McAllister BSC	Chief, Pharmaceutical Operations Directorate
Lt Col Mike Spilker	Consultant to the AF/SG
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Major Jeremy King, MC	Air Force, OB/GYN Physician
Voting Members Absent	
COL Carole Labadie, MS	Army, Pharmacy Officer
CAPT Stephanie Simon, MSC	Navy Pharmacy Officer
Maj William Hannah	Air Force, Internal Medicine
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
COL Kent Maneval, MS	Defense Medical Standardization Board
CDR James Ellzy	DoD P&T Vice Chairman
Ms. Carol Cooper	Deputy General Counsel, TMA
Mr. Jose Ramos *for Maj Peter Trang*	Defense Supply Center Philadelphia
Nonvoting Members Absent	
Mr. William Davies	TRRx/TMOP COR
Guests	
LCDR Joe Bryant	Indian Health Service
Others Present	
RADM Thomas McGinnis via VTC	TMA Pharmacy Operations Directorate
CDR Matthew Carlberg	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
Lt Col Cynthia Lee, BSC	DoD Pharmacoeconomic Center

Appendix A – Attendance – (continued)

LCDR Joe Lawrence	DoD Pharmacoeconomic Center
Maj Joshua Devine, BSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
CAPT Brian Haney	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor
Dr. Roger Potyk	DoD Pharmacy Outcomes Research Team contractor
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor
Dr. Elaine Furmaga	VA PBM
Mr. John Casciotti via teleconference	Office of General Counsel, TMA
Mr. David Hurt	Assistant General Counsel, TMA
Ms. Lisa McNair	DoD Pharmacy Operations Directorate

Appendix B — Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Sildenafil (Viagra) Tadalafil (Cialis) **Phosphodiesterase-5 (PDE-5) Inhibitors**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure • There is no formulary alternative available for patients with pulmonary arterial hypertension (note: does not apply to erectile dysfunction).
Certolizumab injection (Cimzia) Golimumab injection (Simponi) **Targeted Immunomodulatory Biologics (TIBs)**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk
Silodosin capsules (Rapaflo) **Alpha Blockers for BPH**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure. • There is no alternative formulary agent, and the patient requires a drug that can be crushed or sprinkled on food.

Appendix C —Existing Prior Authorization Criteria and Quantity Limits and Recommended PAs and QLs for the Multi-indication Targeted Immunomodulatory Biologics

	Adalimumab (Humira)	Etanercept (Enbrel)	Certolizumab (Cimzia)	Golimumab (Simponi)
Prior Authorization (approved PAs are good indefinitely)	Coverage provided for the treatment of: ▪ Moderately to severely active RA in patients 18 years of age or older. ▪ Active arthritis in patients with PsA 18 years of age or older. ▪ Active AS in patients 18 years of age or older. ▪ Mod to severe active polyarticular JIA (pediatric patients: 4-17 years. ▪ Chronic moderate to severe plaque psoriasis when the patient has tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR is not a candidate for phototherapy or systemic therapy. ▪ Moderately to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to infliximab, or an inability to tolerate infliximab in patients 18 years of age or older. ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, infliximab, abatacept, rituximab, golimumab, or certolizumab.	Coverage provided for the treatment of: ▪ Moderately to severely active RA ▪ Active PsA ▪ Active AS ▪ JRA when the patient has an inadequate response to at least one DMARD ▪ Chronic moderate to severe plaque psoriasis when the patient has tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR is not a candidate for phototherapy or systemic therapy ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, infliximab, 31batacept, rituximab, golimumab, or certolizumab	Coverage provided for the treatment of: ▪ Moderately to severely active rheumatoid arthritis in patients 18 years of age or older. ▪ Moderate to severely active Crohn's Disease following inadequate response to conventional therapy in patients 18 years of age or older. ▪ Coverage NOT provided for concomitant use with abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab or rituximab.	Coverage provided for the treatment of the following conditions in patients 18 years of age or older: ▪ Mod to severe active RA in combination with MTX ▪ Mod to severe active PsA ▪ Active AS ▪ Coverage NOT provided for concomitant use with abatacept, adalimumab, anakinra, certolizumab, etanercept, infliximab or rituximab
Quantity Limits	Retail Network: 4 wks supply (2 packs of 2 syringes) Mail Order: 8 wks supply (4 packs of 2 syringes) Other Issues: Crohn's disease starter pack includes 6 pens for first 4 wks, no refills	Retail Network: 4 wks supply (based on instructions for use) Mail Order: 8 wks supply (based on instructions for use)	Retail Network: 4 wks supply (3 packs of 2 syringes) Mail Order: 8 wks supply (3 packs of 2 syringes) Other Issues: 3 packs of 2 syringes will allow for loading dose at initiation of therapy	Retail Network: 4 wks supply (1 autoinjector or 1 syringe) Mail Order: 8 wks supply (2 auto-injectors or 2 syringes)

AS: ankylosing spondylitis; DMARD: disease-modifying anti-rheumatic drug; JIA: juvenile idiopathic arthritis; JRA: juvenile rheumatoid arthritis; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis

Appendix D — Quantity Limit Updates

Drug	Quantity Limits	Comments
Mometasone (Asmanex Twisthaler) 110 mcg dry powder inhaler	Retail: 2 inhaler/30 days TMOP: 6 inhalers/90 days	Max dose (adults) is 2 puffs/day
Fluticasone (Flovent Diskus) 50-, 100-, and 250 mcg dry powder inhaler	Retail: 1 inhaler/30 days; TMOP: 3 inhalers/90 days	Diskus has 60 doses per inhaler; recommended dose is 1 puff twice daily
Fluoxetine 90 mg (Prozac Weekly)	Retail: 4 capsules/28 days; TMOP: 12 capsules/84 days	Packing issue: each capsule is a 7 day supply with 4 capsules /box for a 28 day supply; will decrease "refill too soon" rejected claims
Azelastine (Astelin) nasal inhaler; Azelastine with sucralose (Astepro) nasal inhaler	Retail: 2 inhalers/30 days TMOP 6 inhalers/90 days	In line with ESI best commercial practices QL applies to both drugs collectively
Tramadol extended release tablets 100-, 200-, and 300 mg(Ryzolt)	Retail: 30 tablets/30 days TMOP: 90 tablets/90 days	Safety issue; consistent with recommended dosing instructions from product labeling

Appendix E — National Defense Authorization Act (NDAA)

Section 703 Affected Medications

A. Drugs Retained as Formulary on the Uniform Formulary			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
ACTIMMUNE	Immunomodulators	INTERMUNE	25
APOKYN	Parkinson's medications	TERCICA INC	47
DERMA-SMOOTHE-FS	Topical corticosteroids	HILL DERM	1,421
DERMOTIC	Otic medications anti-inflammatory	HILL DERM	1,886
INTAL	Mast cell stabilizers, inhalation	KING PHARM	439
PANRETIN	Topical antineoplastic & premalignant lesion medic	EISAI INC.	1
RADIOGARDASE	Radiation exposure (cesium, thallium)	HEYLTEX CORPORA	
STROMECTOL	Antihelmintic	MERCK & CO.	514
THIOLA	Kidney stone agents	MISSION PHARM.	12
VANCOCIN HCL	Misc antibiotics	VIROPHARMA INCO	1,491
B. Drugs moved to or retained as non-formulary on the Uniform Formulary			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
ACIPHEX	PPIs	EISAI INC.	25,129
ACLOVATE	Topical corticosteroids	Pharmaderm	1
AGRYLIN	Platelet reducing agents	SHIRE US INC.	8
ALA-HIST	1st gen AH	POLY PHARM.	216
ALA-HIST D	1st gen AH-decongestant	POLY PHARM.	590
ALTACE	ACE inhibitors	MONARCH PHRM	69
ANAPROX	NSAIDs	ROCHE LABS.	
ANAPROX DS	NSAIDs	ROCHE LABS.	3
ANDROID	Androgens/anabolic steroids	VALEANT	57
APTIVUS	HIV antivirals, protease inhibitors	BOEHRINGER ING.	6
ATROVENT	Nasal anticholinergics	BOEHRINGER ING.	11
ATROVENT HFA	Inhaled anticholinergics	BOEHRINGER ING.	3,565
AZOR	ARB / CCB combo	DAIICHI SANKYO,	4,471
BREVOXYL-4	Keratolytics	STIEFEL LABS.	296
BREVOXYL-8	Keratolytics	STIEFEL LABS.	325

B. Drugs moved to or retained as non-formulary on the Uniform Formulary (cont)			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
BROVEX	1st gen antihistamines	MCR/AMERICAN PH	1
BROVEX CT	1st gen antihistamines	MCR/AMERICAN PH	
BROVEX SR	1st gen AH-decongestant	MCR/AMERICAN PH	
BROVEX-D	1st gen AH-decongestant	MCR/AMERICAN PH	
BUPHENYL	Ammonia inhibitors	MEDICIS DERM	7
CADUET	Statin/CCB combo	PFIZER US PHARM	129
CARBATROL	Anticonvulsants	SHIRE US INC.	1,311
CARNITOR	Metabolic deficiency agents	SIGMA-TAU	15
CARNITOR SF	Metabolic deficiency agents	SIGMA-TAU	2
CATAPRES	Sympatholytics	BOEHRINGER ING.	19
CETROTIDE	LHRH (GNRH) antagonist, pituitary suppressant agent	EMD SERONO, INC	34
CHROMAGEN	Iron replacement	THER-RX	511
CHROMAGEN FORTE	Iron replacement	THER-RX	225
CORDRAN	Topical corticosteroids	AQUA PHARMACEUT	145
CORGARD	Beta blockers	KING PHARM	42
CORTISPORIN	Otic medications, anti-infective	MONARCH PHRM	3
CORTISPORIN	Topical antibiotics & combos	MONARCH PHRM	298
CUTIVATE	Topical corticosteroids	Pharmaderm	1,355
CYTOMEL	Thyroid replacement	KING PHARM	2,955
CYTOXAN	Alkylating agents	BMS ONCO/IMMUN	
DAYTRANA	ADHD medications	SHIRE US INC.	2,700
DECLOMYCIN	Tetracycline	STONEBRIDGE PHA	2
DEGARELIX	Antineoplastic LHRH agonists	FERRING PH INC	
DEPAKENE	Anticonvulsants	ABBOTT LABS.	12
DERMA-SMOOTHE-FS	Topical corticosteroids	HILL DERM	2,239
DIBENZYLINE	Alpha blockers, cardiovascular	WELLSPRING PHAR	46
DIPENTUM	Medications for inflammatory bowel disease	ALAVEN PHARMACE	3
DYNEX 12	antitussive-decongestant	ATHLON PHARM	
DYNEX LA	decongestant-expectorant	ATHLON PHARM	4
DYNEX VR	antitussive-expectorant	ATHLON PHARM	
DYRENIUM	Potassium sparing diuretics	WELLSPRING PHAR	277
ELDEPRYL	Parkinson's medications	SOMERSET PHARM	1

B. Drugs moved to or retained as non-formulary on the Uniform Formulary (cont)			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
ELESTRIN	Estrogens	AZUR PHARMA, IN	26
ELIGARD	Antineoplastic LHRH agonists	SANOFI PHARM	20
EMSAM	MAOIs	BMS PRIMARYCARE	137
ENDOMETRIN	Pregnancy facilitating/maintaining agent	FERRING PH INC	350
ESTRACE	Vaginal estrogen preparations	WC PROF PRODS	8,663
EURAX	Topical antiparasitic	RANBAXY BRAND D	54
EVOXAC	Parasympathetic agents	DAIICHI SANKYO,	1,399
EXELDERM	Topical antifungals	RANBAXY BRAND D	231
FIORICET	Analgesic combos	WATSON PHARMA	300
FLEXERIL	Skeletal muscle relaxants	MC NEIL CONS.	1
FLOMAX	selective alpha blockers for BPH	BOEHRINGER ING.	29,039
FLOXIN	Otic medications, anti-infective	DAIICHI SANKYO,	77
FOSRENOL	Phosphate binders	SHIRE US INC.	635
GESTICARE	Prenatal vitamins	AZUR PHARMA, IN	57
GYNAZOLE-1	Vaginal antifungals	THER-RX	908
HALOG	Topical corticosteroids	RANBAXY BRAND D	261
HEMATRON	Iron replacement	SEYER INC.	22
HEMATRON-AF	Iron replacement	SEYER INC.	131
HYCODAN	antitussive-anticholinergic	ENDO PHARM INC.	
INTELENCE	HIV antivirals, NNRTIs	ORTHO BIOTECH	20
KADIAN	Higher potency single analgesic agents	ALPHARMA BPD	1,512
KAON-CL 10	Potassium replacement	SAVAGE LAB.	35
KAPIDEX	PPIs	TAKEDA PHARM	1,435
KENALOG	Topical corticosteroids	RANBAXY BRAND D	638
KINERET	Targeted immunomodulatory biologics	BIOVITRUM	27
KLONOPIN	Anticonvulsants	ROCHE LABS.	199
K-PHOS NO.2	Urinary pH modifiers	BEACH PRODUCTS	7
K-PHOS ORIGINAL	Urinary pH modifiers	BEACH PRODUCTS	85
KYTRIL	5HT3 antiemetics	ROCHE LABS.	3
LAC-HYDRIN	Emollients	RANBAXY BRAND D	25
LACTINOL	Emollients	PEDINOL PHARM.	13
LACTINOL-E	Emollients	PEDINOL PHARM.	22

B. Drugs moved to or retained as non-formulary on the Uniform Formulary (cont)			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
LEVULAN	Acne meds	DUSA PHARM	
LIALDA	Medications for inflammatory bowel disease	SHIRE US INC.	1,677
LIMBITROL	TCAs & combos	VALEANT	
LITHOSTAT	Ammonia inhibitors	MISSION PHARM.	1
LOCOID	Topical corticosteroids	TRIAX PHARMACEU	
LUVERIS	Luteinizing hormones	EMD SERONO, INC	17
METANX	Vitamin B preparations	PAN AMERICAN	7,475
MICRO-K	Potassium replacement	THER-RX	55
MINOCIN	Tetracyclines	TRIAX PHARMACEU	
MIRAPEX	Parkinson's medications	BOEHRINGER ING.	8,405
MOBIC	NSAIDs	BOEHRINGER ING.	18
MONODOX	Tetracyclines	AQUA PHARMACEUT	2
MS CONTIN	Higher potency single analgesic agents	PURDUE PHARMA L	18
MUSE	Prostaglandins for ED	VIVUS	686
MYAMBUTOL	Antitubercular medications	X-GEN PHARMACEU	1
NEOBENZ MICRO	Keratolytics	SKINMEDICA	223
NIFEREX GOLD	Iron replacement	THER-RX	44
NIFEREX-150 FORTE	Iron replacement	THER-RX	378
NIRAVAM	Anxiolytics	AZUR PHARMA, IN	181
NOVASTART	Prenatal vitamins	AZUR PHARMA, IN	2
NUZON	Topical corticosteroids	WRASER PHARMA	25
OBSTETRIX EC	Prenatal vitamins	SEYER INC.	81
OMNICEF	3rd gen cephalosporins	ABBOTT LABS.	7
OXANDRIN	Androgens/anabolic steroids	SAVIENT PHARMAC	2
OXISTAT	Topical antifungals	Pharmaderm	2,460
OXSORALEN	Hyperpigmentation agents	VALEANT	9
PAMINE	Anticholinergics/antispasmodics	KENWOOD LAB.	4
PAMINE FORTE	Anticholinergics/antispasmodics	KENWOOD LAB.	1
PAMINE FQ	Anticholinergics/antispasmodics	KENWOOD LAB.	2
PCE	Macrolide	ABBOTT LABS.	16
PEDIAPRED	Oral corticosteroids	UCB PHARMA	4

B. Drugs moved to or retained as non-formulary on the Uniform Formulary (cont)			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
PENTASA	Medications for inflammatory bowel disease	SHIRE US INC.	1,553
PERCODAN	Higher potency narcotic analgesic combos	ENDO PHARM INC.	34
PERPHENAZINE	Typical antipsychotics	SANDOZ	356
PERSANTINE	Platelet aggregation inhibitors	BOEHRINGER ING.	4
PHOSLO	Phosphate binders	FRESENIUS MED	24
PLETAL	Platelet aggregation inhibitors	OTSUKA AMERICA	9
POLY HIST DM	antitussive-1st gen AH-decongestant	POLY PHARM.	98
POLY HIST FORTE	1st gen AH-decongestant	POLY PHARM.	514
POLY HIST PD	1st gen AH-decongestant	POLY PHARM.	19
POLY TAN D	1st gen AH-decongestant	POLY PHARM.	63
POLY TAN DM	antitussive-1st gen AH-decongestant	POLY PHARM.	154
POLY-TUSSIN DHC	antitussive-1st gen AH-decongestant	POLY PHARM.	939
POLY-TUSSIN DM	antitussive-1st gen AH-decongestant	POLY PHARM.	132
POTASSIUM CHLORIDE	Potassium replacement	SCHERING CORP G	8,159
PRECARE	Prenatal vitamins	THER-RX	245
PRECARE CONCEIVE	Prenatal vitamins	THER-RX	51
PRECARE PREMIER	Prenatal vitamins	THER-RX	473
PREFERA-OB	Prenatal vitamins	ALAVEN PHARMACE	279
PREMESIS RX	Prenatal vitamins	THER-RX	68
PROAMATINE	Adrenergic vasopressors	SHIRE US INC.	4
PROCRIT	RBC Stimulants	ORTHO BIOTECH	2,201
P-TEX	1st gen antihistamines	POLY PHARM.	
QUIXIN	Ophthalmic antibiotics, quinolones	VISTAKON PHARMA	350
RESPA A.R.	1st gen AH-decongestant-anticholinergic	RESPA PHARM.	503
RESPA-BR	1st gen antihistamines	RESPA PHARM.	85
RHEUMATREX	Antirheumatics	DAVA PHARMACEUT	10
RIOMET	Biguanides	RANBAXY BRAND D	105
SAIZEN	Growth hormone	EMD SERONO, INC	31
SALAGEN	Parasympathetic agents	EISAI INC.	10
SEDAPAP	Analgesic combos	MERZ	
SEPTRA	Sulfonamides/folate antagonists	MONARCH PHRM	

B. Drugs moved to or retained as non-formulary on the Uniform Formulary (cont)			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
SEPTRA DS	Sulfonamides/folate antagonists	MONARCH PHRM	3
SEROSTIM	Growth hormone	EMD SERONO, INC	3
SILVADENE	Topical sulfonamides	MONARCH PHRM	7
SONATA	Newer sedative hypnotics	KING PHARM	282
SORIATANE CK	Psoriasis medications, oral	STIEFEL LABS.	577
SULFAMYLON	Topical sulfonamides	UDL	13
TAPAZOLE	Antithyroid medications	KING PHARM	6
TEMOVATE	Topical corticosteroids	Pharmaderm	4
TEMOVATE EMOLLIENT	Topical corticosteroids	Pharmaderm	2
TENEX	Sympatholytics	PROMIUS PHARMA	19
TESTRED	Androgens/anabolic steroids	VALEANT	72
THALITONE	Thiazides	MONARCH PHRM	29
TIGAN	Other antiemetics	MONARCH PHRM	2
TINDAMAX	Antiprotozoal	MISSION PHARM.	691
TRANSDERM-SCOP	Other antiemetics	BAXTER HEALTHCA	974
TRANSDERM-SCOP	Other antiemetics	NOVARTIS CONSUM	6,163
TRETIN-X	Acne meds	TRIAX PHARMACEU	94
ULTRAVATE	Topical corticosteroids	RANBAXY BRAND D	8
ULTRAVATE PAC	Topical corticosteroids	RANBAXY BRAND D	144
VALIUM	Anxiolytics	ROCHE LABS.	249
VESANOID	Misc antineoplastics	ROCHE LABS.	7
VIRAMUNE	HIV antivirals, NNRTIs	BOEHRINGER ING.	52
VIROPTIC	Ophthalmic antivirals	MONARCH PHRM	5
VYVANSE	ADHD medications	SHIRE US INC.	14,885
WELCHOL	Bile acid sequestrants	DAIICHI SANKYO,	7,541
WESTCORT	Topical corticosteroids	RANBAXY BRAND D	
ZAROXOLYN	Thiazides	UCB PHARMA	9
ZONEGRAN	Anticonvulsants	EISAI INC.	85
ZORBTIVE	Growth hormone	EMD SERONO, INC	

C. Action deferred until November 2009 DoD P&T Committee Meeting			
Product Name	**Subclass**	**Manufacturer**	**Number of Affected Patients**
ARESTIN	Periodontal collagenase inhibitors	ORAPHARMA	
FARESTON	Selective estrogen receptor modulators	GTX INC.	24
GLUCAGEN	Hyperglycemics	BEDFORD LABS	37
GLUCAGEN	Hyperglycemics	NOVO NORDISK	208
GONAL-F	Injectable gonadotropins	EMD SERONO, INC	15
GONAL-F RFF	Injectable gonadotropins	EMD SERONO, INC	160
LEVOTHYROXINE SODIUM	Thyroid replacement	SANDOZ	13,762
PAREMYD	Mydriatics	AKORN INC.	
REBIF	MS-DMDs	EMD SERONO, INC	774
ROZEREM	Newer sedative hypnotics	TAKEDA PHARM	3,835
UROCIT-K	Urinary pH modifiers	MISSION PHARM.	6
VOLTAREN	NSAIDs	ENDO PHARM INC.	16,845

Appendix F — Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (implementation period)
Aug 09 (update; original review Nov 2007)	Targeted Immunomodulatory Biologics	**Recommended for non-formulary status Aug 09; no change to non-formulary status from Nov 07** ▪ golimumab injection (Simponi) ▪ certolizumab injection (Cimzia)	ECF	**No changes to ECF recommendation Nov 07**	pending approval	pending approval
		▪ etanercept injection (Enbrel) ▪ anakinra injection (Kineret)	ECF	▪ adalimumab injection (Humira)	13 Feb 08	18 Jun 08 (120 days)
Aug 09 (update; original review May 05)	Phosphodiesterase Type-5 Inhibitors	**No change to non-formulary status from May 05** Automated PA requiring trial of vardenafil (Levitra) applies to new users of non-formulary PDE5s (no use of PDE5s in last 180 days)	Now BCF	Previously ECF Class ▪ vardenafil (Levitra)	pending approval	pending approval
		▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
Aug 09 (update; updated Nov 07; original review Aug 05)	Alpha Blockers for BPH	**Recommended for non-formulary status Aug 09; no change to non-formulary status from Nov 07 or Aug 05** ▪ silodosin (Rapaflo)	BCF	**No changes to BCF recommendation Nov 07**	pending approval	pending approval
		▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)
Aug 09 (update; updated Nov 07; original review Nov 06)	ADHD / Narcolepsy Agents	**No change to non-formulary status from Aug 05 or Nov 07**	BCF	**No changes to BCF recommendation from Aug 05**	pending approval	pending approval
		Recommended for non-formulary status Nov 07 ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
May 09 (update; reviewed Jun 08; original review May 07)	Antilipidemic Agents-II	**Recommended for non-formulary status May 09; no change to non-formulary status in Jun 08** ▪ fenofibrate acid (Trilipix)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
May 09 update; reviewed Aug 08; Feb 06 original review)	Overactive Bladder Drugs	**Recommended for non-formulary status May 09; no change to non-formulary status in Aug 08** ▪ fesoterodine (Toviaz)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	24 Oct 08	4 Feb 09 (90 days)
May 09 (update; reviewed Nov 08) update to include nasal antihistamines; nasal steroids	Nasal Allergy Drugs	**Recommended for non-formulary status May 09; no change to non-formulary status in Nov 08** ▪ azelastine with sucralose (Astepro)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
reviewed Nov 05 & Aug 07 for Veramyst)		▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ Fluticasone propionate (generic Flonase) ▪ Azelastine (Astelin)	10 Feb 09	8 Apr 09 (60 days)
May 09 (update; reviewed May 07& Feb 05)	Proton Pump Inhibitors	**Recommended for non-formulary status May 09 no change to non-formulary status in May 07** ▪ Dexlansoprazole (Kapidex)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 09 (update; reviewed May 06)	Antiemetics	**Recommended for non-formulary status May 09; no change to non-formulary status in** ▪ granisetron transdermal system (Sancuso)	BCF	No changes to BCF recommendation May 09	17 Aug 09	28 Oct 09
		▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 09	Inhaled Corticosteroids	▪ Beclomethasone HFA MDI (Qvar) ▪ Budesonide MFA MDI (Pulmicort Flexhaler) ▪ Ciclesonide HFA MDI (Alvesco) ▪ Flunisolide CFC MDI (Aerobid, Aerobid M) ▪ Triamcinolone CFC MDI (Azmacort)	BCF	▪ Fluticasone DPI (Flovent Diskus) ▪ Fluticasone HFA MDA (Flovent HFA) ▪ Mometasone DPI (Asmanex Twisthaler)	12 May 2009	16 Sep 09 (120 days)
Feb 09	Long-Acting Beta Agonists	▪ formoterol inhalation solution (Perforomist)	BCF	▪ Salmeterol DPI (Serevent Diskus)	12 May 2009	16 Sep 09 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (implementation period)
Feb 09	Inhaled Corticosteroids / Long-Acting Beta Agonist Combinations	(No ICS/LABA combinations recommended for NF placement Feb 09)	BCF	▪ Fluticasone/salmeterol DPI (Advair Diskus) ▪ Fluticasone/salmeterol HFA MDI (Advair HFA)	12 May 2009	16 Sep 09 (120 days)
Nov 08	Short-Acting Beta Agonists	▪ albuterol chlorofluorocarbon (CFC) metered dose inhaler (MDI) (no longer manufactured) ▪ metaproterenol (Alupent) CFC MDI (no longer marketed) ▪ metaproterenol inhalation solution ▪ pirbuterol (Maxair) MDI	BCF	▪ Ventolin HFA (albuterol hydrofluoroalkane (HFA) MDI ▪ Albuterol inhalation solution; Note – does not include the following: Accuneb 0.021% [0.63 mg/mL] Accuneb 0.042% [1.25 mg/3mL] Albuterol 0.5% [2.5 mg/0.5 mL in 0.5 unit dose vial]	10 Feb 09	8 Apr 09 (60 days)
Nov 08 & Aug 08 (update; reviewed Nov 05)	Antidepressants I	**Recommended for non-formulary status Aug 08; no change to non-formulary status in Nov 08** ▪ desvenlafaxine (Pristiq)	BCF	No changes to BCF recommended Aug 08	10 Feb 09; original signing date 24 Oct 08	7 Jan 09 (60 days)
		To remain NF ▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg weekly admin. (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen & special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Nov 08	ACE inhibitors – Renin Angiotensin Antihypertensives	Previously non-formulary, recommended for UF status Nov 08 ▪ ramipril (Altace generic)	BCF	▪ No changes recommended to BCF at Nov 08 meeting; ramipril removed from Non-formulary status and designated as Uniform Formulary immediately upon signing of the minutes	10 Feb 09	N/A
Oct 08 (interim teleconference meeting) & Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	24 Oct 08;; original signing date: 27 Aug 08	26 Nov 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	▪ OneTouch Ultra 2 strips (for OneTouch Ultra 2, Ultra Mini, and Ultra Smart meters) ▪ TrueTrack strips (for TrueTrack meter) ▪ Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) ▪ Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check ▪ Plus all other store/private label brand strips not included on the UF (see BCF/ECF column)	BCF	**Basic Core Formulary SMBGS test strips** ▪ Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	24 Oct 08	17 Mar 09 (120 days)
Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	**Recommended for non-formulary status Aug 08** ▪ nisoldipine geomatrix (Sular geomatrix)	BCF	No changes to BCF recommended Aug 08	24 Oct 08	7 Jan 09 (60 days)
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR, ER (Dynacirc; Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER HS dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (implementation period)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)		▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** ▪ Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ zileuton (Zyflo)		Currently BCF ▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives,	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** ▪ olmesartan/amlodipine (Azor)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (implementation period)
including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update		To remain NF ▪ valsartan amlodipine (Exforge)		No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ Moexipril +/- HCTZ (Univasc; Uniretic) ▪ perindopril (Aceon) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) (D/C'd from market) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan+/- HCTZ (Avapro, Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- (Diovan; Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel, generics) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / noreth. 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	▪ selegiline transdermal patch (Emsam)	ECF	▪ phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	**Recommended for non-formulary status Nov 06:** 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)
		▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)		▪ nystatin ▪ clotrimazole	17 Jan 07	18 Mar 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
CFC = chlorofluorocarbon; ER = extended release; HFA = hydrofluoroalkane; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle;
AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MDIs = metered dose inhalers; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; NADs = Nasal Allergy Drugs; OABs = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SABAs = Short-Acting Beta Agonists; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones
*The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix G — Table of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder drug class
AE	adverse event
APR	Automated profile review
AS	ankylosing spondylitis
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BPH	benign prostatic hyperplasia
BIA	budget impact analysis
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations
CHCS	Composite Health Care System
CMA	cost minimization analysis
CPAP	continuous positive airway pressure
DoD	Department of Defense
ECF	Extended Core Formulary
ED	erectile dysfunction
ER	extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
IPSS	International Prostate Symptom Score
MHS	Military Health System
MN	medical necessity
MSLT	mean sleep latency testing
MTF	Military Treatment Facility
MTX	methotrexate
NDAA	National Defense Authorization Act
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAH	pulmonary arterial hypertension
PDE-5	Phosphodiesterase-type 5 inhibitor drug class
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
POS	point of service
PsA	psoriatic arthritis
QL	quantity limit
Qmax	maximum urine flow rate
RA	rheumatoid arthritis
SQ	subcutaneous
TBI	traumatic brain injury
TIB	Targeted Immunomodulatory Drug Class
TNF-α	Tumor necrosis factor alpha
TFL	TRICARE for life beneficiary
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
May 2009

1) CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened a web conference at 10:00 on May 13, 2009.

2) ATTENDANCE

The attendance roster is found in Appendix A.

3) REVIEW MINUTES OF LAST MEETINGS

A. Revisions to the minutes—Revisions to the February 2009 minutes will be reviewed at the August 2009 DoD P&T Committee meeting.

B. Approval of February minutes—Ms. Ellen P. Embrey, performing the duties of the Assistant Secretary of Defense, Health Affairs, approved the minutes of the November 2008 DoD P&T Committee meeting on May 12, 2009.

4) REVIEW OF RECENTLY FDA-APPROVED AGENTS

A. Antilipidemic-II Agents (LIP-2)—Fenofibrate acid capsules (Trilipix)

Relative Clinical Effectiveness—Fenofibrate acid (Trilipix) is the choline salt of fenofibrate; the active moiety is the same as the other fenofibrate formulations. The fenofibrates are classified in the Antilipidemic-II (LIP-2) drug class that was reviewed for Uniform Formulary (UF) placement in May 2007. Fenofibrate acid is Food and Drug Administration (FDA)-approved for use as monotherapy, and in combination with a statin to lower triglycerides (TGs) and increase high density lipoprotein (HDL) cholesterol in patients with coronary heart disease (CHD) or CHD risk equivalent to those who are receiving optimal statin therapy.

The fenofibrate acid (Trilipix) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, Title 32, Code of Federal Regulations (CFR), Section 199.21(e)(1). There are no comparative clinical trials between fenofibrate acid and the other LIP-2 drugs, and no trials evaluating outcomes other than changes in lipid parameters. The clinical trials used to obtain FDA approval reported fenofibrate acid combined with either a low-dose or moderate-dose statin resulted in additive effects on raising HDL cholesterol and lowering TGs, compared to the statin administered alone. The safety profile of fenofibrate acid reflects that of the other fenofibrate products.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) that although fenofibrate acid (Trilipix) is the only fenofibrate drug specifically approved by the FDA for use in combination with a statin, there was insufficient evidence to compare its safety in combination with a statin versus the other fenofibrates. The P&T Committee concluded fenofibrate acid (Trilipix) did not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other fenofibrate formulations currently included on the UF because they all contain the same active ingredient.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of fenofibrate acid capsules (Trilipix) in relation to efficacy, safety, tolerability, and clinical outcomes of other agents in the class, particularly to the following LIP-2 medications: micronized fenofibrate (Lofibra/generic), fenofibrate meltdose (Fenoglide), and nanomicronized fenofibrate (Tricor). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of fenofibrate acid capsules (Trilipix) relative to other UF LIP-2s. Results from the CMA showed the projected weighted average cost per day for fenofibrate acid capsules (Trilipix) is higher than fenofibrate micronized (Lofibra/generics) and fenofibrate meltdose (Fenoglide). The CMA also revealed the projected weighted average cost per day for fenofibrate acid capsules (Trilipix) is slightly lower than the non-formulary LIP-2 agent, nanomicronized fenofibrate (Tricor). Micronized fenofibrate (Lofibra/generic) and fenofibrate meltdose (Fenoglide) remain the most cost effective LIP-2 agents on the UF compared to fenofibrate acid capsules (Trilipix).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 0 absent) that fenofibrate acid capsules (Trilipix) are not cost effective relative to other formulary LIP-2 agents.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) fenofibrate acid capsules (Trilipix) be designated non-formulary on the UF. This

recommendation was based on the clinical effectiveness conclusion and the determination that micronized fenofibrate (Lofibra/generic) and fenofibrate meltdose (Fenoglide) remain the most cost effective LIP-2 agents on the UF compared to fenofibrate acid capsules (Trilipix).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of fenofibrate acid capsules (Trilipix) and the conditions for establishing medical necessity (MN) of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for fenofibrate acid capsules (Trilipix). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at military treatment facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

B. Overactive Bladder Drugs—Fesoterodine extended release (ER) tablets (Toviaz)

Relative Clinical Effectiveness—The muscarinic antagonist fesoterodine (Toviaz) is a prodrug that undergoes conversion by plasma esterases to the same active metabolite as tolterodine (Detrol, Detrol LA). Like the other OAB

drugs, fesoterodine extended release (ER) tablets are FDA-approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency. The OAB drug class was previously reviewed for UF placement in August 2008 and February 2006.

The fesoterodine ER tablets (Toviaz) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). There are no direct comparative clinical trials between fesoterodine ER and the other OAB drugs. Statistically significant improvements in the endpoints of urinary frequency, urge urinary incontinence, and urinary urgency vs. placebo were noted in the clinical trials used to obtain FDA approval. The incidence of dry mouth and constipation reported with fesoterodine ER 8 milligrams (mg) was higher than tolterodine ER (Detrol LA) 4 mg in the one indirect active comparator trial available. Product labeling states that fesoterodine does not prolong the QT interval.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) fesoterodine ER tablets (Toviaz) did not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other OAB drugs currently included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of fesoterodine ER tablets (Toviaz) in relation to efficacy, safety, tolerability, and clinical outcomes of other agents in the class, particularly to oxybutynin XL (Detrol XL/generics), tolterodine LA (Detrol LA), solifenacin (Vesicare), and darifenacin (Enablex). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of fesoterodine (Toviaz) relative to other UF OABs. Results from the CMA showed the projected weighted average cost per day for fesoterodine (Toviaz) is higher than other UF OABS.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) fesoterodine ER tablets (Toviaz) are not cost effective relative to other formulary OAB agents.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) that fesoterodine ER tablets (Toviaz) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of fesoterodine ER tablets (Toviaz) and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for fesoterodine extended release (ER) tablets (Toviaz). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

C. Nasal Allergy Drugs (NADs)—Azelastine with sucralose nasal spray (Astepro)

Relative Clinical Effectiveness—Azelastine with sucralose nasal spray (Astepro) is a Nasal Allergy Drug (nasal antihistamine) containing the same active ingredient (azelastine) and dosage strength as Astelin nasal spray. Sucralose and sorbitol have been added to the Astepro formulation to help mask the bitter taste reported with Astelin. Astepro is FDA-approved for treating seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Astelin has additional indications (SAR in patients ≥5 years, and non-allergic rhinitis). The Nasal Allergy Drugs (NADs) were previously reviewed for UF placement in November 2008.

The azelastine with sucralose nasal spray (Astepro) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). One unpublished study reported statistically significant improvements in nasal congestion, rhinorrhea, sneezing, and nasal itching with both Astepro and Astelin, compared to the placebo vehicle. The improvements in nasal symptoms were similar with Astepro and Astelin. Bitter taste and epistaxis are the adverse events reported most frequently with Astepro.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) azelastine with sucralose nasal spray (Astepro) does not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other NADs currently included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of azelastine with sucralose nasal spray (Astepro) in relation to efficacy, safety, tolerability, and clinical outcomes of the other nasal antihistamine subclass agents in the NAD class, particularly to azelastine (Astelin) and olopatadine (Patanase). Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of azelastine with sucralose nasal spray (Astepro) relative to other nasal antihistamine subclass agents in the NAD class. Results from the CMA showed the projected weighted average cost per day for azelastine with sucralose nasal spray (Astepro) is higher than azelastine (Astelin) but less than olopatadine (Patanase), which is a non-formulary medication.

Relative Cost-Effectiveness Conclusion–P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 0 abstained, 1 absent) that azelastine with sucralose nasal spray (Astepro) is not cost effective relative to other UF nasal antihistamine subclass agents in the NAD class.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (12 for, 1 opposed, 0 abstained, 0 absent) that azelastine with sucralose nasal spray (Astepro) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of azelastine with sucralose nasal spray (Astepro) and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for azelastine with sucralose nasal spray (Astepro). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and

2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. Proton Pump Inhibitors—Dexlansoprazole delayed release capsules (Kapidex)

Relative Clinical Effectiveness—The Proton Pump Inhibitor (PPI) dexlansoprazole (Kapidex) is a sustained-release formulation of the R-enantiomer of lansoprazole (Prevacid). Generic formulations of lansoprazole are anticipated in late 2009. The PPIs were reviewed for UF placement in May 2007 and February 2005.

The dexlansoprazole delayed release (DR) capsules (Kapidex) evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). Dexlansoprazole DR capsules are FDA-approved for use in adults for healing of erosive esophagitis (EE), maintenance of EE healing, and gastroesophageal reflux disease. Lansoprazole (Prevacid) has additional FDA-approved indications. The clinical studies used to obtain FDA-approval compared dexlansoprazole DR 60 mg capsules with lansoprazole 30 mg capsules or with placebo; there are no studies directly comparing the drug with other PPIs. The most common adverse events with dexlansoprazole DR capsules are diarrhea, nausea, and abdominal pain, which are similar to the other PPIs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) dexlansoprazole DR capsules (Kapidex) did not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other PPI drugs currently included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of dexlansoprazole DR capsules (Kapidex) in relation to efficacy, safety, tolerability, and clinical outcomes of selected UF agents in the PPI class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the cost-effectiveness of dexlansoprazole DR capsules (Kapidex) relative to selected PPIs, including omeprazole (Prilosec) and esomeprazole (Nexium). Results from the CMA showed the projected weighted average cost per day for dexlansoprazole DR capsules (Kapidex) is higher than all other comparators.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 0 absent) that dexlansoprazole DR capsules (Kapidex) are not cost effective relative to other formulary PPI agents.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) that dexlansoprazole DR capsules (Kapidex) be designated non-formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of dexlansoprazole DR capsules (Kapidex) and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for dexlansoprazole DR capsules (Kapidex). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee voted (13 for, 0 opposed, 0 abstained, 0 absent) to recommend 1) an effective date of the first Wednesday 1 week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and 2)

TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

E. Antidepressant-1 Agents—Venlafaxine Extended Release Tablets

Relative Clinical Effectiveness—Relative Clinical Effectiveness—Venlafaxine is a serotonin norepinephrine reuptake inhibitor (SNRI) antidepressant. The Antidepressant-I (AD-1) drug class was reviewed for UF placement in November 2005. Venlafaxine Extended Release (ER) Tablets (brand name) contain the same active ingredient as venlafaxine ER capsules (Effexor XR), but employ a different mechanism to extend the dosing interval. The FDA does not consider Venlafaxine ER Tablets an AB-rated generic formulation of Effexor XR capsules. Venlafaxine ER Tablets and Effexor XR capsules are not considered therapeutically interchangeable by the FDA due to the different marketed dosage formulations (i.e., capsule vs. tablet). AB-rated generic formulations of Effexor XR capsules are expected in 2010–2011. Venlafaxine ER Tablets have demonstrated bioequivalence with Effexor XR capsules in pharmacokinetic studies.

The Venlafaxine ER Tablets clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). Venlafaxine ER Tablets are FDA-approved for treating Major Depressive Disorder and Social Anxiety Disorder; Effexor XR has additional indications. No clinical trials have been conducted with Venlafaxine ER Tablets. Venlafaxine ER Tablets were FDA-approved under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, based on demonstrated bioequivalence with Effexor XR. Adverse events with Venlafaxine ER Tablets reflect those contained in the Effexor XR product labeling.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (12 for, 1 opposed, 0 abstained, 0 absent) there was no evidence to suggest there are clinically relevant differences in the efficacy, safety, and clinical outcomes of Venlafaxine ER Tablets compared to Effexor XR capsules because both products contain the same active ingredient.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of Venlafaxine ER Tablets in relation to efficacy, safety,

tolerability, and clinical outcomes of selected formulary SSRIs and other SNRI subclass agents in the AD-1 class. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e) (2).

CMA was used to evaluate the relative cost-effectiveness of Venlafaxine ER Tablets relative to selected SSRIs, particularly to sertraline (Zoloft/generics) citalopram (Celexa/generics), and other SNRI subclass agents in the AD-1 class. The SNRIs reviewed in the CMA were venlafaxine ER capsules (Effexor XR), duloxetine (Cymbalta), and desvenlafaxine (Pristiq). Results from the CMA showed the projected weighted average cost per day for Venlafaxine ER Tablets is higher than both SSRIs reviewed. The CMA also revealed Venlafaxine ER Tablets are the most cost-effective agent in the SNRI subclass.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 0 absent) that Venlafaxine ER Tablets are cost effective relative to other UF SNRI subclass agents in the AD-1 class.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) that Venlafaxine ER Tablets remain formulary on the UF.

Acting Director, TMA, Decision ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: BCF RECOMMENDATION***—Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 0 abstained, and 0 absent) to recommend Venlafaxine ER Tablets not be added to the BCF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

F. Antiemetics—Granisetron transdermal system (Sancuso)

Relative Clinical Effectiveness—The granisetron transdermal system (TDS) (Sancuso) is a serotonin subtype-3 (5-HT3) receptor antagonist. It is the only newer antiemetic available in a transdermal dosage form. Granisetron (Kytril, generics) is also available in tablets, an oral solution, and intravenous formulation. The newer antiemetics were evaluated for UF placement in May 2006.

Granisetron TDS is FDA-approved for the prevention of nausea and vomiting in adult patients receiving moderately or highly emetogenic chemotherapy regimens lasting for ≤5 consecutive days. Other newer antiemetics (granisetron and ondansetron [Zofran, generics]) have indications in addition to chemotherapy-induced nausea and vomiting (CINV).

The granisetron TDS (Sancuso) clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1). In clinical studies, granisetron TDS has shown non-inferiority (but not superiority) to oral granisetron in controlling nausea and vomiting associated with CINV. There is insufficient evidence to determine whether granisetron TDS would control nausea and vomiting to a greater extent than the other 5-HT3 antagonists. There are no studies evaluating differences in the adverse events between granisetron TDS and 5-HT3 antagonists other than oral granisetron.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (13 for, 0 opposed, 0 abstained, 0 absent) although granisetron TDS (Sancuso) is the only newer antiemetic available in a transdermal formulation, it does not have a significant, clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other newer antiemetics currently included on the UF.

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of granisetron TDS (Sancuso) in relation to efficacy, safety, tolerability, and clinical outcomes of selected UF agents in the antiemetic class. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e) (2).

CMA was used to evaluate the relative cost-effectiveness of granisetron TDS (Sancuso) relative to ondansetron (Zofran/generics) oral and oral dissolving tablets and granisetron (Kytril/generics) tablets. Results from the CMA showed the projected weighted average cost per week for granisetron TDS (Sancuso) is higher than all other comparators.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 0 absent) that granisetron TDS (Sancuso) is not cost effective relative to other antiemetic agents.

1) ***COMMITTEE ACTION: UF RECOMMENDATION***—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 0 abstained, 0 absent) granisetron TDS (Sancuso) be designated as non-formulary on the UF.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

2) ***COMMITTEE ACTION: MN CRITERIA***—Based on the clinical evaluation of granisetron TDS (Sancuso) and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 0 absent) MN criteria for granisetron TDS (Sancuso). (See Appendix B for full MN criteria).

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P. Embrey

*3) **COMMITTEE ACTION: IMPLEMENTATION PERIOD***—The P&T Committee voted (11 for, 0 opposed, 0 abstained, 2 absent) to recommend 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: Ellen P Embrey

5) UTILIZATION MANAGEMENT—PRIOR AUTHORIZATIONS (PA) / Quantity Limits (QL) / MEDICAL NECESSITY (MN)

A. PPI—Prior Authorization / Medical Necessity Criteria (MN): The P&T Committee reviewed current published literature, national guidelines/expert consensus statements, and FDA guidance related to reports of a drug interaction between clopidogrel (Plavix) and PPIs, and the corresponding potential for decreased antiplatelet effect and adverse cardiovascular outcomes. An automated prior authorization (APR) or *step therapy* is currently in effect and requires use of UF generic omeprazole or esomeprazole (Nexium) before other non-formulary PPIs, unless there is therapeutic failure, intolerance, or hypersensitivity. MN criteria also applies to non-formulary PPIs. The P&T Committee concluded the evidence was not sufficient at this time to recommend a change in the current PA/MN criteria, but agreed with continued monitoring of the literature for possible changes to the PA/MN criteria.

1) ***COMMITTEE ACTION:*** The Committee voted (12 for, 0 opposed, 1 abstained, 0 absent) to recommend no change to the existing PPI PA/MN criteria.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. QL Updates: In anticipation of the forthcoming TPHARM contract implementation, the P&T Committee updated the quantity limits (QLs) for several drugs. See Appendix C.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (11 for, 0 opposed, 0 abstained, 2 absent) to recommend the QLs for ondansetron (Zofran), dasatinib (Sprycel), budesonide nebulizer solution (Pulmicort Respules), cromolyn inhaler (Intal), azelastine nasal spray (Astelin), azelastine with sucralose nasal spray (Astepro), metaproterenol nebulizer solution (Alupent, generics), ipratropium/albuterol inhaler (Combivent), methylnaltrexone subcutaneous injection (Relistor), as outlined in Appendix C.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. **Extended Core Formulary (ECF) Clarification**—The P&T Committee was briefed in August 2008 on efforts to implement electronic prescribing in the Military Health System (MHS). As part of the ongoing plan to systematically review drugs represented on the Basic Core Formulary (BCF)/Extended Core Formulary (ECF), the P&T Committee periodically reviews recommendations for changes to the BCF/ECF. At this meeting, the ECF was reviewed because greater specificity in the drug listings is required to assist with e-prescribing efforts. Appendix D outlines drugs currently designated as ECF.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (11 for, 0 opposed, 1 abstained, 1 absent) to recommend the listing of the ECF drugs, as outlined in Appendix D.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. **Oral Fentanyl Citrate Automated PA**—The P&T Committee was briefed on an analysis examining MHS utilization of oral fentanyl citrate buccal lozenges (Actiq) and buccal tablets (Fentora) among opioid-naïve patients (i.e., those without prior opioid exposure). Both Actiq and Fentora are indicated for breakthrough pain in combination with long-acting opioids in opioid-tolerant patients. A total of 1,217 TRICARE beneficiaries received prescriptions for oral fentanyl citrate during the 5-month observation period from November 1, 2009 to May 31, 2009. The oral fentanyl prescriptions were dispensed in majority (89 percent) from the TRRx. Forty percent of patients (492/1,217) were identified as new oral fentanyl citrate users. A total of 375 (76 percent) new users received an opioid prescription within the last 60-days of their first oral fentanyl citrate prescription; 81 percent of new users had prior exposure to a strong opioid. In total, 10 percent (117/1,217) of all oral fentanyl citrate users were opioid-naïve. Sensitivity analysis showed results to be dependent on length of look-back period.

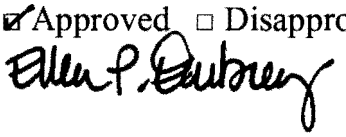
Due to potential patient safety and inappropriate prescribing concerns, the P&T Committee recommended inclusion of oral fentanyl citrate products (Actiq and Fentora) in the current Automated Profile Review (APR) for transdermal fentanyl. The APR is available at retail and mail order points of service and allows pharmacists to override the requirement for evidence of a previous opioid prescription in the 60-day look- back period with intervention and outcome codes (to avoid disrupting chronic therapy). The fentanyl APR

process differs from other PAs that require review by ESI (Express Scripts, Inc., DoD contractor for retail and mail order), have more stringent criteria to allow overrides, and take longer to resolve. The Pharmacy Program Office has requested and will begin testing a similar function in the Composite Health Care System for the MTF pharmacies.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (11 for, 0 opposed, 0 abstained, 2 absent) to recommend addition of the oral formulations of fentanyl citrate, Actiq and Fentora be added to the automated PA.

Acting Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:



6) FUTURE UF DRUG CLASS REVIEWS

A drug class overview for the Phosphodiesterase type-5 inhibitors (PDE-5s) was presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the Pharmacoeconomic Center to use in completing the clinical effectiveness reviews and developing appropriate cost-effectiveness models. The clinical and economic analyses of this drug class will be completed for August 2009 P&T Committee meeting.

7) ITEMS FOR INFORMATION

A. **National Defense Authorization Act (NDAA) Section 703—Inclusion of TRICARE Retail Pharmacy Program in Federal Procurement of Pharmaceuticals Update**—The Office of General Counsel (OGC) updated the P&T Committee on the litigation and status of the final rule that will implement Section 703 of the 2008 NDAA. The judge has not rendered a decision regarding the current litigation. The final rule is at the Office of Management and Budget (OMB). Key members from the TMA Pharmacy Operations Department and OGC have met with OMB personnel. The timetable for approval and impact on the DoD P&T Committee process are not known.

8) ADJOURNMENT

The meeting adjourned at 3:00 on March 13, 2009. The next meeting will be in August 2009.

Appendix A—Attendance
Appendix B—Table of Medical Necessity Criteria
Appendix C—Table of Quantity Limits
Appendix D—Table of Extended Core Formulary Clarification
Appendix E—Table of Implementation Status of UF Recommendations/Decisions
Appendix F—Table of Abbreviations

SUBMITTED BY:

17 Aug 09

COL John Kugler, MC, USA
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Acting Director, TMA, decisions are as annotated above.

Ellen P. Embrey
Performing the Duties of the
Assistant Secretary of Defense,
Health Affairs

08/17/09
(Date)

Appendix A — Attendance

Voting Members Present	
COL John Kugler, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	DoD P &T Committee Recorder
COL Doreen Lounsbery , MC	Army, Internal Medicine Physician, Alternate
COL Peter Bulatao *for Col Isiah Harper, MSC*	Army, Pharmacy Officer, Alternate
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
LTC Bruce Lovins	Army, Family Practice Physician, Alternate
CDR Walter Downs, MC	Navy, Internal Medicine Physician, Alternate
CDR David Tanen, MC	Navy, Physician at Large
Lt Col Thomas Bacon, BSC *for Col Everett McAllister*	Chief, Pharmaceutical Operations Directorate
Lt Col Michael Lee, BSC *for Col Mark Butler*	Consultant to the AF/SG
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Major Jeremy King, MC	Air Force, OB/GYN Physician
Voting Members Absent	
COL Carole Labadie, MS	Army, Pharmacy Officer
COL Ted Cieslak, MC	Army, Physician at Large
Mr. Joe Canzolino	Department of Veterans Affairs
Nonvoting Members Present	
CDR James Ellzy	DoD P&T Vice Chairman
Mr. David Hurt	Deputy General Counsel, TMA
Nonvoting Members Absent	
COL Kent Maneval, MS	Defense Medical Standardization Board
Mr. William Davies	TRRx/TMOP COR
Maj Peter Trang	Defense Supply Center Philadelphia
Guests	
LCDR Tracie Patten *for CDR Robert Hayes*	Indian Health Service
Others Present	
CDR Matthew Carlberg	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
MAJ Misty Carlson, MC	DoD Pharmacoeconomic Center
LCDR Joe Lawrence	DoD Pharmacoeconomic Center

Appendix A — Attendance — (continued)

Others Present	
Maj Joshua Devine, BSC	DoD Pharmacoeconomic Center
LCDR Marisol Martinez	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Teresa Anekwe	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacoeconomic Center
Dr. Brian Beck	DoD Pharmacy Operations Center contractor
Dr. Dean Valibhai	DoD Pharmacy Operations Center contractor
Dr. Carl R. Summers	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Dr. Roger Potyk	DoD Pharmacy Outcomes Research Team contractor
Mr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B — Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Azelastine with sucralose nasal spray (Astepro) **Nasal Allergy Drugs (NADs)**	• Use of formulary alternatives is contraindicated
Dexlansoprazole delayed release capsules (Kapidex) **Proton Pump Inhibitors (PPIs)**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives.
Fenofibrate acid delayed release capsules (Trilipix) **Antilipidemic-II Drugs (LIP-2s)**	• Use of formulary alternatives is contraindicated
Fesoterodine extended release tablets (Toviaz) **Overactive Bladder Drugs (OABs)**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives.
Granisetron transdermal system (Sancuso) **Antiemetics**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

Appendix C — Quantity Limit Updates

Drug	TMOP QL	TRRx QL	Comments
Ondansetron (Zofran) 24 mg tablets	3 tabs/Rx	1 tab/Rx	-Indicated for single dose highly emetogenic chemo; -Not studied in multiple-day regimens -Other strengths of ondansetron are available for delayed nausea and vomiting
Dasatinib (Sprycel) 100 mg tablets	90 tabs/45 days	60 caps / 30 days	-Starting dose is 100mg/d -Max dose is 200mg/d in advanced phase CML -Therapy is continued until disease worsens or patient can't tolerate
Budesonide (Pulmicort Respules) nebulizer soln 1 mg/ml	180 ml (90 ampules) / 90 days	60 ml (30 ampules) / 30 days	Max dose is 1 mg (2ml) per day
Cromolyn (Intal) inhaler 8.1 gm	9 inhalers / 90 days	3 inhalers / 30 days	112 puffs/inhaler, max 240 inhalations/month
Azelastine (Astelin) nasal spray	6 bottles / 90 days	2 bottles / 30 days	Clarified TMOP quantity for consistency
Azelastine with sucralose (Astepro) nasal spray	6 bottles / 90 days	2 bottles/30 days	New product in already reviewed class
Metaproterenol nebulizer solution	600 amps / 90 days	200 amps/30 days	Max dose based on labeling
Ipratropium /albuterol (Combivent) inhaler 14.7 gm	6 inhalers / 90 days	2 inhalers/30 days	Max dose based on labeling
Methylnaltrexone SQ Injection (Relistor)	No Refills	No Refills	Intended for palliative care

Appendix D — Extended Core Formulary Clarification

Therapeutic Category	Generic Name	Brand Name	Dosage	Dosage Form	P&T Meeting
ANTIARTHRITICS	ADALIMUMAB	HUMIRA	40 MG/0.8ML	KIT	Nov 2007 & Feb 2008
AUTONOMIC DRUGS	DONEPEZIL HCL	ARICEPT	10 MG	TABLET	Nov 2005
AUTONOMIC DRUGS	DONEPEZIL HCL	ARICEPT	5 MG	TABLET	Nov 2005
UNCLASSIFIED DRUG PRODUCTS	INTERFERON BETA-1A	AVONEX	30 MCG/.5ML	KIT	May 2005
PSYCHOTHERAPEUTIC DRUGS	PHENELZINE SULFATE	NARDIL	15 MG	TABLET	Feb 2007
HORMONES	SOMATROPIN	NORDITROPIN	5 MG/1.5ML	CARTRIDGE	Aug 2007
HORMONES	SOMATROPIN	NORDITROPIN NORDIFLEX	5 MG/1.5ML	PEN INJCTR	Aug 2007
HORMONES	SOMATROPIN	NORDITROPIN NORDIFLEX	10 MG/1.5ML	PEN INJCTR	Aug 2007
HORMONES	SOMATROPIN	NORDITROPIN	15 MG/1.5ML	CARTRIDGE	Aug 2007
HORMONES	SOMATROPIN	NORDITROPIN NORDIFLEX	15 MG/1.5ML	PEN INJCTR	Aug 2007
UNCLASSIFIED DRUG PRODUCTS	VARDENAFIL HCL	LEVITRA	5 MG	TABLET	May 2005
UNCLASSIFIED DRUG PRODUCTS	VARDENAFIL HCL	LEVITRA	10 MG	TABLET	May 2005
UNCLASSIFIED DRUG PRODUCTS	VARDENAFIL HCL	LEVITRA	20 MG	TABLET	May 2005

Appendix E — Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 09 (update; reviewed Jun 08; original review May 07)	Antilipidemic Agents-II	**Recommended for non-formulary status May 09; no change to non-formulary status in Jun 08** ▪ fenofibrate acid (Trilipix)	BCF	No changes to BCF recommendation May 09	pending approval	pending approval
Jun 08 (update; reviewed May 07)	Antilipidemic - Agents II	No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
May 09 update; reviewed Aug 08; Feb 06 original review)	Overactive Bladder Drugs	**Recommended for non-formulary status May 09; no change to non-formulary status in Aug 08** ▪ fesoterodine (Toviaz)	BCF	No changes to BCF recommendation May 09	pending approval	pending approval
Aug 08 (re-review; Feb 06 original review)	Overactive Bladder (OAB) Agents	▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	24 Oct 08	4 Feb 09 (90 days)
May 09 (update; reviewed Nov 08)	Nasal Allergy Drugs	**Recommended for non-formulary status May 09; no change to non-formulary status in Nov 08** ▪ azelastine with sucralose (Astepro)	BCF	No changes to BCF recommendation May 09	pending approval	pending approval

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 08 (update to include nasal antihistamines; nasal steroids reviewed Nov 05 & Aug 07 for Veramyst)	Nasal Allergy Drugs	▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ Fluticasone propionate (generic Flonase) ▪ Azelastine (Astelin)	10 Feb 09	8 Apr 09 (60 days)
May 09 (update; reviewed May 07& Feb 05)	Proton Pump Inhibitors	**Recommended for non-formulary status May 09 no change to non-formulary status in May 07** ▪ Dexlansoprazole (Kapidex)	BCF	No changes to BCF recommendation May 09	pending approval	pending approval
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 09 (update; reviewed May 06)	Antiemetics	**Recommended for non-formulary status May 09; no change to non-formulary status in** ▪ granisetron transdermal system (Sancuso)	BCF	No changes to BCF recommendation May 09	pending approval	pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 09	Inhaled Corticosteroids	▪ Beclomethasone HFA MDI (Qvar) ▪ Budesonide MFA MDI (Pulmicort Flexhaler) ▪ Ciclesonide HFA MDI (Alvesco) ▪ Flunisolide CFC MDI (Aerobid, Aerobid M) ▪ Triamcinolone CFC MDI (Azmacort)	BCF	▪ Fluticasone DPI (Flovent Diskus) ▪ Fluticasone HFA MDA (Flovent HFA)	12 May 2009	16 Sep 09 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Feb 09	Long-Acting Beta Agonists	▪ formoterol inhalation solution (Perforomist)	BCF	▪ Salmeterol DPI (Serevent Diskus)	12 May 2009	16 Sep 09 (120 days)
Feb 09	Inhaled Corticosteroids / Long-Acting Beta Agonist Combinations	(No ICS/LABA combinations recommended for NF placement Feb 09)	BCF	▪ Fluticasone/salmeterol DPI (Advair Diskus) ▪ Fluticasone/salmeterol HFA MDI (Advair HFA)	12 May 2009	16 Sep 09 (120 days)
Nov 08	Short-Acting Beta Agonists	▪ albuterol chlorofluorocarbon (CFC) metered dose inhaler (MDI) (no longer manufactured) ▪ metaproterenol (Alupent) CFC MDI (no longer marketed) ▪ metaproterenol inhalation solution ▪ pirbuterol (Maxair) MDI	BCF	▪ Ventolin HFA (albuterol hydrofluoroalkane (HFA) MDI ▪ Albuterol inhalation solution; Note – does not include the following: Accuneb 0.021% [0.63 mg/mL] Accuneb 0.042% [1.25 mg/3mL] Albuterol 0.5% [2.5 mg/0.5 mL in 0.5 unit dose vial]	10 Feb 09	8 Apr 09 (60 days)
Nov 08 (update to include nasal antihistamines; nasal steroids reviewed Nov 05 & Aug 07 for Veramyst)	Nasal Allergy Drugs	▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ Fluticasone propionate (generic Flonase) ▪ Azelastine (Astelin)	10 Feb 09	8 Apr 09 (60 days)
Nov 08 & Aug 08 (update; reviewed Nov 05)	Antidepressants I	**Recommended for non-formulary status Aug 08; no change to non-formulary status in Nov 08** ▪ desvenlafaxine (Pristiq)	BCF	No changes to BCF recommended Aug 08	10 Feb 09; original signing date 24 Oct 08	7 Jan 09 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 08 (update; reviewed Nov 05)	Antidepressants I	To remain NF ▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg weekly admin. (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen & special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Nov 08	ACE inhibitors – Renin Angiotensin Antihypertensives	Previously non-formulary, recommended for UF status Nov 08 ▪ ramipril (Altace generic)	BCF	▪ No changes recommended to BCF at Nov 08 meeting; ramipril removed from Non-formulary status and designated as Uniform Formulary immediately upon signing of the minutes	10 Feb 09	N/A
Oct 08 (interim teleconference meeting) & Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	24 Oct 08;; original signing date: 27 Aug 08	26 Nov 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	▪ OneTouch Ultra 2 strips (for OneTouch Ultra 2, Ultra Mini, and Ultra Smart meters) ▪ TrueTrack strips (for TrueTrack meter) ▪ Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) ▪ Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check ▪ Plus all other store/private label brand strips not included on the UF (see BCF/ECF column)	BCF	**Basic Core Formulary SMBGS test strips** ▪ Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	24 Oct 08	17 Mar 09 (120 days)
Aug 08 (re-review; Feb 06 original review)	Overactive Bladder (OAB) Agents	▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	24 Oct 08	4 Feb 09 (90 days)
Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	**Recommended for non-formulary status Aug 08** ▪ nisoldipine geomatrix (Sular geomatrix)	BCF	No changes to BCF recommended Aug 08	24 Oct 08	7 Jan 09 (60 days)
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR, ER (Dynacirc; Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER HS dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)		▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** ▪ Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ zileuton (Zyflo)		Currently BCF ▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** ▪ olmesartan/amlodipine (Azor)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ valsartan amlodipine (Exforge)		No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ Moexipril +/- HCTZ (Univasc; Uniretic) ▪ perindopril (Aceon) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) (D/C'd from market) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan+/- HCTZ (Avapro, Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- (Diovan; Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel, generics) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / noreth. 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)		▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan +/-HCTZ (Avapro; Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- HCTZ (Diovan; Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	▪ selegiline transdermal patch (Emsam)	ECF	▪ phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	**Recommended for non-formulary status Nov 06:** 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)		▪ nystatin ▪ clotrimazole	17 Jan 07	18 Mar 07 (60 days)
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06 (re-classified Aug 07; and updated Jun 08; see above)	Misc Antihypertensive Agents (ACE/CCB combos now part of RAAs class)	(ACE/CCB combos now part of RAAs class) ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	(ACE/CCB combos now part of RAAs class) ▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
May 05	PDE5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary CFC = chlorofluorocarbon; ER = extended release; HFA = hydrofluoroalkane; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle; AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MDIs = metered dose inhalers; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; NADs = Nasal Allergy Drugs; OABs = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SABAs = Short-Acting Beta Agonists; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones *The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])						

Appendix F — Table of Abbreviations

5-HT3	serotonin subtype 3
AE	adverse event
APR	Automated profile review
AD-1	Antidepressant-I drug class
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations
CHCS	Composite Health Care System
CHD	coronary heart disease
CINV	chemotherapy induced nausea and vomiting
CMA	cost minimization analysis
DoD	Department of Defense
DR	delayed release
ECF	Extended Core Formulary
EE	erosive esophagitis
ESI	Express Scripts, Inc
ER	extended release
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HDL	high density lipoprotein
LIP-2	Antilipidemic-II drug class
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
NAD	Nasal Allergy drug class
NDAA	National Defense Authorization Act
OAB	Overactive Bladder drug class
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
PPI	Proton Pump Inhibitor drug class
PDE-5	Phosphodiesterase-type 5 inhibitor drug class
QL	quantity limit
SAR	seasonal allergic rhinitis
SNRI	serotonin norepinephrine reuptake inhibitor
TDS	transdermal system
TFL	TRICARE for life beneficiary
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
February 2009

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 18 February 2009 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

The attendance roster is found in Appendix A.

3. REVIEW MINUTES OF LAST MEETINGS

A. Revisions to the minutes — There were no revisions to the November 2008 DoD P&T Committee meeting minutes.

B. Approval of November minutes — S. Ward Casscells, III, MD, approved the minutes of the November 2008 DoD P&T Committee meeting on 10 February 2009.

4. REVIEW OF RECENTLY FDA-APPROVED AGENTS

Self-Monitored Blood Glucose System (SMBGS) Test Strips — TRUETest Test Strip

Relative Clinical Effectiveness — The self-monitored blood glucose system (SMBGS) test strips were evaluated for Uniform Formulary (UF) placement at the August 2008 DoD P&T Committee meeting. The other SMBGS test strips designated as formulary on the UF include Accu-chek Aviva, Precision Xtra, Freestyle Lite, and Ascensia Contour. The TRUEtest SMBGS test strip was approved by the FDA in late August 2008 and, therefore, was not included in the original UF decision. The TRUEtest test strip clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1).

The TRUEtest SMBGS test strip meets the requirements for accuracy by the FDA and the International Standard for Organization, does not require coding, is compatible with 2 SMBGS meters (TRUEresult and TRUE2go meters), requires a 0.5 microliter blood sample size, is approved for both fingertip and forearm testing, and provides results in 4 to 10 seconds. The TRUEtest SMBGS test strip employs glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) as the reagent. Other SMBGS test strips with GDH-PQQ have been rarely associated with falsely high blood glucose readings and potential patient harm when used concurrently with products containing maltose (e.g., dialysis patients receiving icodextrin dialysate solutions). The TRUEtest package label contains warnings for this interaction.

Relative Clinical Effectiveness Conclusion — The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent): 1) the TRUEtest SMBGS test strip is similar to other SMBGS test strips included on the UF, in terms of meeting the minimum technical requirements; 2) there is a high degree of therapeutic interchangeability between TRUEtest and the other SMBGS test strips included on the UF; and 3) in

terms of safety, TRUEtest is similar to other SMBGS test strips included on the UF that also use the GDH-PQQ reagent.

Relative Cost-Effectiveness — The P&T Committee evaluated the relative cost-effectiveness of TRUEtest SMBGS test strips in relation to efficacy, safety, tolerability, and clinical outcomes of the other test strips in the SMBGS class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost-effectiveness of TRUEtest blood glucose strips. The cost-effectiveness of TRUEtest was evaluated relative to the following agents: Accu-chek Aviva, Contour, Freestyle Lite, OneTouch Ultra, Precision Xtra, and TrueTrack. The results of the CMA showed that the projected weighted average daily cost of TRUEtest was significantly lower than the weighted average daily cost of all the other SMBGS test strips.

Relative Cost-Effectiveness Conclusion — The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 0 absent) that the TRUEtest SMBGS test strip for the TRUEresult and TRUE2go meters is cost effective relative to the other SMBGS test strips included on the UF when future market conditions were considered.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 0 opposed, 1 abstained, 0 absent) that the TRUEtest SMBGS test strip remain designated as formulary on the UF.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: BCF RECOMMENDATION*** — Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 0 absent) to recommend: 1) the TRUEtest test strips not be added to the BCF.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

5. DRUG CLASS REVIEW — PULMONARY I AGENTS — INHALED CORTOCOSTEROIDS (ICS)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the inhaled corticosteroids (ICS) as part of the Pulmonary I drug

class. The ICS are available in several dosage formulations, including pressurized metered-dose inhalers (MDIs) and dry powder inhalers (DPIs). The MDIs use either chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) as the propellant. The ICS available as oral inhalers include beclomethasone HFA MDI (QVAR), budesonide DPI (Pulmicort Flexhaler), ciclesonide HFA MDI (Alvesco), flunisolide CFC MDI (Aerobid, Aerobid-M [menthol added to improve taste]), fluticasone HFA MDI (Flovent HFA), fluticasone DPI (Flovent Diskus), mometasone DPI (Asmanex Twisthaler), and triamcinolone CFC MDI (Azmacort). Budesonide (Pulmicort Respules) is also available as an inhalation solution.

The current ICS Basic Core Formulary (BCF) products are budesonide inhalation solution (Pulmicort Respules as the specified product), fluticasone oral inhaler, and triamcinolone oral inhaler. None of the oral ICS inhalers are available as generic formulations. One authorized generic formulation of budesonide inhalation solution became available in December 2008.

The US Food and Drug Administration (FDA) recommended the removal of ICS metered-dose inhalers containing a CFC propellant (flunisolide and triamcinolone) by 31 December 2009. A final decision regarding this proposed date is pending.

The Military Health System (MHS) spent over $35M on oral ICS inhalers and over $13M on ICS inhalation solutions in FY 2008. In FY 2008, for the oral ICS inhalers, expenditures in the Military Treatment Facilities (MTFs) were $16.6M, expenditures in the TRICARE Retail Network (TRRx) were $15.2M, and expenditures in the TRICARE Mail Order Pharmacy (TMOP) were $3.5M. Expenditures for the inhalation solutions in FY 2008 are as follow: MTF $2.4M, TRRx $10.0M, and TMOP $0.8M. In terms of numbers of prescriptions dispensed, fluticasone (Flovent) is the highest utilized ICS in the MHS, followed by triamcinolone (Azmacort).

Information regarding the safety, effectiveness, and clinical outcomes of the ICS was considered by the Committee. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the pharmaceutical agents included on the UF in that therapeutic class.

Relative Clinical Effectiveness Conclusion — The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent), as part of the Pulmonary I overall relative clinical effectiveness conclusion, to accept the following regarding the clinical effectiveness of the ICS products:

A. With regard to efficacy/clinical effectiveness of the ICS, the following conclusions were made:

- FDA-approved indications — The Committee recognized that the ICS products are approved only for the maintenance treatment of asthma, and FDA-approved age ranges for pediatric patients differ between the products.

- Clinical Practice Guidelines — Evidence-based guidelines from the National Asthma Education and Preventive Program (NAEPP) consider the ICS the preferred treatment for the maintenance treatment of persistent asthma. Guidelines for the use of ICS in Chronic Obstructive Pulmonary Disease (COPD) generally recommend an ICS for severe or very severe disease. The Guidelines do not state a preference for one ICS over another.
- Pharmacodynamic/pharmacokinetic properties — The Committee concluded that despite differences in topical potency, receptor binding affinity, pulmonary bioavailability, and systemic bioavailability, the overall clinical response does not appear to vary significantly between the ICS, when equipotent doses are compared.
- Overall clinical efficacy for asthma — The Committee concluded that for asthma, there is fair-to-moderate evidence that ICS do not differ with regards to symptom control, need for rescue medication, and exacerbations in patients with asthma.
- Overall clinical efficacy for COPD — The Committee concluded that for COPD, there is insufficient evidence to conclude there are clinically relevant differences regarding the efficacy of ICS in patients with COPD.

B. With regards to safety and tolerability, the following conclusions were made:

- Minor adverse events — There do not appear to be clinically relevant differences in the incidence and severity of common adverse events associated with the ICS, such as dysphonia and oral candidiasis.
- Pharmacodynamic/pharmacokinetic properties — Differences in binding affinity, lipophilicity, pulmonary bioavailability, and systemic bioavailability between the ICS products have not correlated to clinically relevant differences in safety.
- Systemic adverse effects — For systemic adverse effects of hypothalamic-pituitary-adrenal (HPA) axis suppression, growth suppression, cataract formation, fracture risk, and pneumonia risk in COPD, there is insufficient evidence to determine whether one ICS is more likely to cause these effects than another. When given in recommended doses, the ICS are not generally associated with clinically significant systemic adverse effects. Providers and patients must assess the risks and benefits if higher than recommended doses are required.
- Overall safety/tolerability — The Committee concluded there is insufficient evidence to determine whether there are clinically relevant differences between ICS in terms of minor adverse events or systemic adverse events

C. With regards to differences in other factors, the following conclusions were made:

- Special Populations – Pregnancy — Budesonide is the only ICS with a pregnancy category B rating (low evidence of risk) from the FDA; the other ICS are rated pregnancy category C. The pregnancy category B rating for

budesonide was granted based on information from 3 Swedish registries and 1 prospective study. However, national guidelines for asthma from the NAEPP state there is no data to indicate the other ICS preparations are unsafe during pregnancy, and that untreated asthma in pregnancy poses a risk to the fetus, including intrauterine growth retardation, premature delivery, and low birth weight.

- Special Populations – Children — Budesonide inhalation solution (Pulmicort Respules) is approved for treating asthma in children ranging between the ages of 1 and 8 years. Fluticasone (Flovent Diskus and Flovent HFA) and mometasone (Asmanex) are approved for treating asthma in children 4 years of age and older.
- Clinical Coverage — Responses from a survey of MTF providers revealed that to meet the needs of the majority of MHS beneficiaries, both HFA metered-dose inhalers and dry powder inhalers are required for inclusion on the UF.
- Therapeutic Interchangeability — There is a high degree of therapeutic interchangeability between the ICS products.

Relative Cost-Effectiveness — In considering the relative cost-effectiveness of pharmaceutical agents in the ICS as part of the Pulmonary I class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) and budget impact analysis (BIA) were used to evaluate the cost-effectiveness of the ICS.

ICS Relative Cost-Effectiveness Conclusion — Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

A. Results of the CMA revealed that beclomethasone DPI (QVAR) was the most cost-effective ICS based on acquisition cost; and

B. Results of the BIA revealed that the ICS formulary scenario that included budesonide inhalation solution, fluticasone HFA metered-dose inhaler (Flovent HFA), fluticasone dry powder inhaler (Flovent DPI), and mometasone dry powder inhaler (Asmanex Twisthaler) was the most cost-effective overall.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) to accept the cost-effectiveness conclusions stated above.

2) ***COMMITTEE ACTION: UF RECOMMENDATION*** — In view of the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the ICS products and other relevant factors, the P&T

Committee, based upon its collective professional judgment, voted (8 for, 5 opposed, 2 abstained, 0 absent) to recommend:

a) Budesonide inhalation solution (Pulmicort Respules, generic), fluticasone HFA MDI (Flovent HFA), fluticasone DPI (Flovent Diskus), and mometasone DPI (Asmanex Twisthaler) be classified as formulary under the UF; and

b) Beclomethasone HFA MDI (QVAR), budesonide DPI (Pulmicort Flexhaler), ciclesonide HFA MDI (Alvesco), flunisolide CFC MDI (Aerobid, Aerobid M) and triamcinolone CFC MDI (Azmacort) be designated as non-formulary on the UF, based on cost-effectiveness.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** — Based on the clinical evaluation for beclomethasone HFA MDI (QVAR), budesonide DPI (Pulmicort Flexhaler), ciclesonide HFA MDI (Alvesco), flunisolide CFC MDI (Aerobid, Aerobid M), triamcinolone CFC MDI (Azmacort), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for beclomethasone HFA MDI (QVAR), budesonide DPI (Pulmicort Flexhaler), ciclesonide HFA MDI (Alvesco), flunisolide CFC MDI (Aerobid, Aerobid M) and triamcinolone CFC MDI (Azmacort). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** — The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent): 1) an effective date of the first Wednesday one week following a 120-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 120-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin the first Wednesday one week following approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

5) ***COMMITTEE ACTION: BCF RECOMMENDATION*** — The P&T Committee considered the BCF status of the ICS agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted 14 for, 0 opposed, 1 abstained, 0 absent) to recommend: 1) fluticasone HFA MDI and DPI (Flovent HFA and Flovent Diskus) oral inhalers remain designated as BCF; and 2) mometasone DPI (Asmanex Twisthaler) be designated as BCF immediately upon signing of the February 2009 DoD P&T Committee minutes by the Director, TMA. As a result of the above actions, budesonide inhalation solution (Pulmicort Respules) would no longer be designated as BCF, but maintained as formulary on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW — PULMONARY I AGENTS – LONG-ACTING BETA AGONISTS (LABAs)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the long-acting beta agonists (LABAs), as part of the Pulmonary I drug class. The LABAs include 2 DPIs, salmeterol (Serevent Diskus) and formoterol (Foradil Aerolizer), and 2 inhalation solutions, formoterol solution (Perforomist) and arformoterol solution (Brovana). There are no generic formulations available for the LABAs. The current BCF LABA is salmeterol DPI (Serevent Diskus).

MHS expenditures for the LABAs in FY 2008 in the entire MHS exceeded $9.1M ($1.6M in the MTFs, $5.8M in the TRRx, and $1.7M in the TMOP). Salmeterol DPI (Serevent Diksus) is the most frequently used LABA in the entire MHS with approximately 250,000 prescriptions dispensed monthly. However overall, there is a trend for decreasing LABA use in the MHS.

Relative Clinical Effectiveness Conclusion — The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent), as part of the Pulmonary I overall relative clinical effectiveness conclusion, to accept the following regarding the clinical effectiveness of the LABA products:

A. With regard to efficacy/clinical effectiveness between the LABA oral inhalers, salmeterol DPI (Serevent Diskus) and formoterol DPI (Foradil Aerolizer), the following conclusions were made:

- FDA-approved indications — Salmeterol and formoterol have similar FDA-approved indications (asthma, COPD, and exercise-induced bronchospasm [EIB]), with the exception that their pediatric-approved ages for asthma differ.
- Pharmacokinetics — Formoterol has a faster onset of action than salmeterol, but clinical efficacy is similar for changes in forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF).

- Guidelines — Evidence-based guidelines from the NAEPP for asthma and the Global Initiative for Obstructive Lung Disease (GOLD) for COPD do not state a preference for one LABA over another.
- Asthma — For treating asthma, both salmeterol and formoterol have been shown to reduce the occurrence of asthma symptoms and reduce the need for rescue medications, when compared to placebo. Head-to-head studies show no difference between salmeterol and formoterol in relieving asthma symptoms, reduced use of rescue medications, or improvement in spirometry measures.
- COPD and EIB — There is insufficient evidence to determine if clinically relevant differences exist when treating COPD or EIB.

B. With regard to efficacy/clinical effectiveness between the LABA-inhaled solutions, formoterol solution (Perforomist), and arformoterol solution (Brovana), the following conclusions were made:

- COPD — There is insufficient evidence to determine if clinically relevant differences exist when treating COPD.
- Place in therapy — The LABA inhalation solutions are relatively new additions to the market. Recommendations regarding their most appropriate use in patients with COPD have not been discussed in national guidelines.

C. With regard to safety between the LABA oral inhalers, salmeterol DPI (Serevent Diskus), and formoterol DPI (Foradil Aerolizer):

- In patients with asthma, a higher risk of death was associated with salmeterol and formoterol use. This is based on data from the Salmeterol Multicenter Asthma Research Trial, an FDA meta-analysis conducted in 2008, and 2 Cochrane reviews. The risk of death is highest in subpopulations of African American patients and children 4 to 11 years of age. Using a LABA with an ICS reduces the risk of death in asthma. The FDA Advisory subcommittee is recommending removal of the LABA indication for asthma. These recommendations are pending approval at the FDA.
- In patients with COPD, 1 meta-analyses (Rodrigo 2008) and 1 pooled analysis have reported no increased risk of death with salmeterol or formoterol.
- For other serious adverse events, there do not appear to be clinically relevant differences between salmeterol and formoterol, based on similar numbers needed to harm (188 vs. 179, respectively) from 2 Cochrane reviews.

D. With regard to safety between the LABA-inhaled solutions, formoterol solution (Perforomist) and arformoterol solution (Brovana) for treating COPD, there is insufficient evidence to determine if clinically relevant differences exist in the adverse effect profile. The LABA-inhaled solutions are not approved for treating asthma.

E. With regard to other factors between the LABAs, the following conclusions were made:

- Ease of use: The formoterol DPI (Foradil Aerolizer) is more difficult for patients to use than salmeterol DPI (Serevent Diskus).
- Special Populations: For asthma, salmeterol is approved for a younger patient population (approved for children as young as 4 years old) compared to formoterol (approved for children as young as 5 years old).
- Storage conditions: Storage conditions are more favorable with formoterol inhalation solution (Perforomist), which is stable at room temperature for up to 12 weeks vs. 6 weeks with arformoterol inhalation solution (Brovana).
- Clinical Coverage: A survey of MTF providers showed that the majority of respondents require a LABA oral inhaler to treat their patients with COPD.
- Therapeutic Interchangeability: The Committee concluded there is a high degree of therapeutic interchangeability between the two LABA inhalation solutions and, with the exception of convenience/ease of use, there is a high degree of therapeutic interchangeability between the two LABA oral inhalers.
- Use of LABAs without concomitant use of ICS in MHS:
  - Results of a preliminary analysis reported by the Pharmacy Outcomes Research Team (PORT) indicated that of the 13,533 DoD beneficiaries who filled at least 1 prescription for a LABA during a 6-month study period (June – November 2008) at any DoD point of service, 6,118 (45%) had not filled a prescription for an ICS or an ICS/LABA combination during the 180 days prior to or the 60 days following the date of their first LABA prescription during the study period. The pronounced skew in this group toward older ages (mean: 69 years [SD 14]; median age: 72 years) and the fact that about 30% had filled an anticholinergic prescription during the same time period suggested a predominantly COPD population. Patients under 55 years of age who had not filled an anticholinergic prescription (characteristics suggesting asthma rather than COPD) made up only about 11% (655 patients) of this group. The analysis included both new and previous LABA users. It did not control for use of other health insurance or starting/stopping TRICARE coverage, both of which could result in missing data regarding concomitant ICS use.
  - The Committee agreed that the great majority of DoD beneficiaries receiving LABAs without concomitant ICS are probably COPD patients, in whom "unopposed" use of LABAs has not been associated with safety concerns, and that the absolute number of asthma patients in this category is likely to be small. However, they suggested that further analysis utilize asthma or COPD diagnoses (e.g., medical claims data or patient records) to identify patient groups and that available data be analyzed to investigate anecdotal reports of asthmatic patients discontinuing use of ICS without the knowledge of their providers after being placed on a LABA (either

because of greater perceived symptom relief or because of the difficulty of keeping up with multiple inhalers).

Relative Cost-Effectiveness — In considering the relative cost-effectiveness of pharmaceutical agents in the LABAs as part of the Pulmonary I class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) and budget impact analysis (BIA) were used to evaluate the cost-effectiveness of the LABAs.

LABA Relative Cost-Effectiveness Conclusion — Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

A. Results of the CMA of the LABA oral inhalers revealed that formoterol DPI (Foradil Aerolizer) was the most cost-effective LABA oral inhaler overall;

B. Results of the CMA of the LABA inhalation solutions revealed that arformoterol solution (Brovana) was the most cost-effective overall; and

C. The BIA evaluated the potential impact of scenarios with selected LABA agents designated formulary or non-formulary on the UF. Results from the BIA revealed that the scenario that designated formoterol inhalation solution (Perforomist) non-formulary under the UF was most favorable to the MHS.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) to accept the cost-effectiveness conclusions stated above.

2) ***COMMITTEE ACTION: UF RECOMMENDATION*** — In view of the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the LABA products and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend that:

   1. Salmeterol DPI (Serevent Diskus), formoterol DPI (Foradil Aerolizer) and arformoterol inhalation solution (Brovana) be classified as formulary under the UF; and

   2. Formoterol inhalation solution (Perforomist) be designated as non-formulary on the UF, based on cost-effectiveness.

Director, TMA, Decision: Ellen P. Embrey ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: MN CRITERIA*** — Based on the clinical evaluation for formoterol inhalation solution (Perforomist) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) MN criteria for formoterol inhalation solution (Perforomist). (See Appendix B for full MN criteria).

Director, TMA, Decision: Allen P. Aubrey ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** — The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent): 1) an effective date of the first Wednesday one week following a 120-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 120-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin the first Wednesday one week following approval by the Director, TMA.

Director, TMA, Decision: Allen P. Aubrey ☑ Approved ☐ Disapproved

Approved, but modified as follows:

5) ***COMMITTEE ACTION: BCF RECOMMENDATION*** — The P&T Committee considered the BCF status of the LABA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 2 abstained and 0 absent) to recommend that salmeterol DPI (Serevent Diskus) remain designated as BCF.

Director, TMA, Decision: Allen P. Aubrey ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW — PULMONARY I AGENTS – INHALED CORTICOSTEROID / LONG-ACTING BETA AGONIST COMBINATIONS (ICS/LABA COMBINATIONS)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the ICS/LABA combinations, as part of the Pulmonary I drug class. There are 2 ICS/LABA combinations available. Fluticasone/salmeterol (Advair Diskus) is available as both a dry powder inhaler and as an HFA metered-dose inhaler (Advair HFA). Budesonide/formoterol (Symbicort) is available as an HFA metered-dose inhaler. MHS expenditures for the ICS/LABA combinations exceeded $153M

in FY 2008 (MTF $55.2M, TRRx $75.1M, TMOP $23.4M). In terms of number of prescriptions dispensed, fluticasone/salmeterol DPI (Advair Diskus) is by far the highest utilized ICS/LABA across all 3 points of service. The current BCF product is fluticasone/salmeterol (Advair).

Relative Clinical Effectiveness Conclusion — The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent), as part of the Pulmonary I overall relative clinical effectiveness conclusion, to accept the following regarding the clinical effectiveness of the ICS/LABA combination oral inhalers:

A. With regard to efficacy/clinical effectiveness between the ICS/LABA oral inhalers, the following conclusions were made:

- FDA-approved Indications — The Committee recognized that the ICS/LABA combinations are all approved for the long-term treatment of asthma, and that pediatric age ranges differ between the products. Additionally, fluticasone/salmeterol DPI (Advair Diskus) dry powder inhaler is FDA-approved to reduce air flow obstruction and reduce exacerbations in COPD. These FDA indications for COPD apply only to the fluticasone 250 mcg /salmeterol 50 mcg Advair Diskus dosage strength. Note: Following the meeting on 27 Feb 2009, the FDA approved formoterol/budesonide DPI (Symbicort) for treating COPD.

- Efficacy/clinical effectiveness for asthma — The Committee concluded that there was fair evidence to suggest that there are no clinically relevant differences in efficacy between fluticasone/salmeterol and budesonide/formoterol for the treatment of asthma. This is based on the conclusions of 2 systematic reviews (Cochrane and the state of Oregon Drug Effectiveness Review Project) and head-to-head trials showing similar improvements in PEF, mean reduction of asthma exacerbations, and increases in the percentage of symptom-free days.

- Efficacy/clinical effectiveness for COPD — The Committee concluded that there was insufficient evidence to determine whether there are clinically relevant differences in efficacy between fluticasone/salmeterol and budesonide/formoterol for the treatment of COPD.

B. With regard to safety/tolerability:

- Product labeling — The Committee recognized that the safety information contained in the product labeling for the ICS/LABA combinations closely reflects the product labels for the individual ICS and LABA components.

- Minor adverse events — Comparative trials of the ICS/LABA combinations show that the products are generally well-tolerated. The most common adverse events are nasopharyngitis, headache, upper respiratory infection, oral candidiasis, and dysphonia. Adverse events for ICS/LABA combination are similar to those reported with an equipotent dose of the individual ICS component.

C. With regard to other factors between the ICS/LABA combination oral inhalers:

- Clinical Coverage – The Committee concluded that, to meet the needs of the majority of MHS beneficiaries, MHS providers require availability of both a metered-dose inhaler and dry powder inhaler formulation of the ICS/LABA combinations.
- Therapeutic Interchangeability — The Committee concluded that there is a high degree of therapeutic interchangeability between fluticasone/salmeterol (Advair) and budesonide/formoterol (Symbicort).
- DoD Persistence Data —
    - The PORT reported preliminary results of an analysis of persistence on treatment among DoD beneficiaries who are new users of ICS/LABA combinations (Advair or Symbicort). The study sample consisted of 3,857 patients randomly sampled from the population of DoD beneficiaries who 1) received at least 1 prescription for an ICS/LABA combination from 1 Jul 2007 to 31 Dec 2007; 2) had not received an ICS/LABA prescription in the last 365 days; 3) were between 12–55 years of age (to focus on use in adults and adolescents with asthma); and 4) were enrolled in TRICARE Prime or Plus with prescription coverage throughout the study. Persistence was measured as percentage of days covered (PDC) over 1 year. Based on ICD-9 diagnosis codes from medical claims data during the baseline and accrual periods and prescription fills for anticholinergics (indicative of COPD), 72% of the study sample had a diagnosis of asthma and 12% had a diagnosis of COPD or had received an anticholinergic prescription, with 8% of patients falling into both groups. Of the remaining 24% (n=920), about two-thirds had diagnoses for acute respiratory illness and/or allergic rhinitis, while about one-third did not have a claim coded for any study diagnosis.
    - Persistence was low compared to those found for other chronic medications, with a mean PDC over 1 year of 28.3% (SD 25.2%). Overall, only 7% of patients had a PDC of at least 80% (i.e., a cumulative days supply of at least 292 days), while 16% had a PDC of at least 50%. These findings were influenced by patients who received only an initial ICS/LABA prescription (47%), with no other fills during the 365-day follow-up period. Notably, the percentage of patients receiving only 1 ICS/LABA prescription was greatest (69%) among the 920 patients without an asthma or COPD diagnosis, compared to about 40% among the 2,957 patients who did not have asthma or COPD diagnosis. This group was also less likely than the asthma or COPD groups to be treated with any other controller medication (ICS, LABAs, leukotrienes, methylxanthines, or anticholinergics). These results suggest that a considerable proportion of ICS/LABA use may be for acute rather than chronic conditions.
    - The Committee suggested that MTFs may wish to review appropriateness of ICS/LABA combination use at their facilities,

particularly with regard to acute vs. chronic use. They also agreed that formulary management documents sent to MTFs should call attention to the potential for low persistence among new users of ICS/LABAs, even those diagnosed with chronic conditions such as asthma or COPD. They agreed with plans for further analysis in this area.

Relative Cost-Effectiveness — In considering the relative cost-effectiveness of pharmaceutical agents in the ICS/LABA combination oral inhalers as part of the Pulmonary I class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) and budget impact analysis (BIA) were used to evaluate the cost-effectiveness of the ICS/LABA combinations.

LABA Relative Cost-Effectiveness Conclusion — Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

A. Results of the CMA of the ICS/LABA combination oral inhalers revealed that budesonide/ formoterol (Symbicort) was the most cost-effective combination inhaler agent overall; and

B. The BIA evaluated the potential impact of scenarios with selected ICS/LABA combination agents designated formulary or non-formulary on the UF. Results from the BIA revealed that the scenario that designated budesonide/ formoterol (Symbicort) inhaler non-formulary (with an automated prior authorization) under the UF was most favorable to the MHS.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) to accept the cost-effectiveness conclusions stated above.

2) ***COMMITTEE ACTION: UF RECOMMENDATION*** — In view of the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the ICS/LABA combination products and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 2 opposed, 1 abstained, 0 absent) to recommend that:

   1. Fluticasone/salmeterol HFA (Advair HFA) and DPI (Advair Diskus) and budesonide/formoterol (Symbicort) inhaler be classified as formulary on the UF; and

   2. That no ICS/LABA combination agents be designated as non-formulary under the UF, based on cost-effectiveness.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: BCF RECOMMENDATION*** — The P&T Committee considered the BCF status of the ICS/LABA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained and 1 absent) to recommend that fluticasone/salmeterol DPI (Advair Diskus) and fluticasone/salmeterol HFA MDI (Advair HFA) remain designated as BCF immediately on signing of the February 2009 DoD P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8. UTILIZATION MANAGEMENT — PRIOR AUTHORIZATIONS (PA) / Quantity Limits (QL) / MEDICAL NECESSITY (MN)

A. Nasal Allergy Drugs — Quantity Limits (QLs): The Nasal Allergy Drugs were reviewed for UF placement at the November 2008 DoD P&T Committee meeting. The class is comprised of the nasal inhaled corticosteroids, nasal antihistamines, and nasal anticholinergic agents. The 2 newest products in the class are the nasal corticosteroid ciclesonide (Omnaris) and the nasal antihistamine olopatadine (Patanase). QLs are in place for the other members of the nasal allergy drug class, which take into account FDA-approved dosing. The Committee recommended QLs for ciclesonide and olopatadine nasal inhalers, consistent with the other members in the class.

1) ***COMMITTEE ACTION:*** The Committee voted (13 for, 1 opposed, 1 abstained, 0 absent) to recommend quantity limits for ciclesonide nasal inhaler (Omnaris) of 6 bottles per 90 days in the TMOP, and 2 bottles per 30 days in the TRRx; and for olopatadine nasal inhaler (Patanase) of 6 bottles per 90 days in the TMOP, and 2 bottles per 30 days in the TRRx.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Fluticasone/salmeterol Oral HFA MDI (Advair HFA) — QLs: The ICS/LABA combination oral inhalers have QLs in place that take into account FDA-approved dosing and safety information. The fluticasone/salmeterol oral DPI (Advair Diskus) has current QLs of 3 inhalers (180 doses) per 90 days in the TMOP, and 1 inhaler (60 doses)/30 days in the TRRx.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend QLs for fluticasone/salmeterol HFA MDI (Advair HFA) of 2 inhalers per 30 days in the TRRx, and 6 inhalers per 90 days in the TMOP.

Director, TMA, Decision: Ellen P. Embrey ☑ Approved ☐ Disapproved
Approved, but modified as follows:

C. **Antifungal Prior Authorization** — The prior authorization (PA) was reviewed for terbinafine (Lamisil and generics), itraconazole (Sporanox and generics) and ciclopirox lacquer (Penlac and generics). The PA was placed due to the high cost of the drugs and potential hepatotoxic adverse effects. With the introduction of generic products, the price of the drugs has significantly fallen. COL Trinka Coster, MD, from the Pharmacovigilance Center presented data that indicated the rates for signals for these drugs in the safety databases were very low.

1) ***COMMITTEE ACTION:*** The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend removing the Antifungal Prior Authorization requirement for terbinafine (Lamisil), itraconazole (Sporonax), and ciclopirox nail lacquer (Penlac).

Director, TMA, Decision: Ellen P. Embrey ☑ Approved ☐ Disapproved
Approved, but modified as follows:

9. ITEMS FOR INFORMATION

A. **Ezetimibe / Simvastatin (Vytorin) Safety Update** — LtCol James McCrary provided the Committee with an update on recent safety information for ezetimibe/simvastatin (Vytorin). The Antilipidemic I class, which includes the statins, ezetimibe, niacin and their combination products, will be re-reviewed for UF status at an upcoming meeting

B. **MTF and TMOP Pricing Update** — Contracts for products with Federal Supply Schedule prices are in the review stage of the contract cycle. The contracts are reviewed at the Veteran's Administration National Acquisition Center (VA NAC). As of 1 February 2009, the VA NAC had completed 200 out of 246 contract reviews. Drug manufacturers are able to adjust prices due to changes in market conditions. A review of the impact of price changes on spending indicated that spending in the MTFs could increase by approximately 7% and spending at the TMOP point of service could increase by 6%. These price changes should have little effect on spending in TRRx.

C. **Patient Safety / Pharmacovigilance** — COL Coster provided the Committee with information on data mining in the Adverse Event Reporting System (AERS) database. The goal of data mining is to detect increased signals of adverse events that can be further evaluated for significance. Definitions and term hierarchy of the Medical Dictionary for Regulated Activities were presented. Limitations were discussed; e.g., no denominator data, missing data, drug name errors, underreporting, over reporting

due to publicity, lack of consistent diagnostic criteria. AERS data mining information will be presented during initial drug class committee presentations.

D. Extended Core Formulary (ECF) — The PEC had previously briefed the Committee on efforts to implement electronic prescribing in the MHS. As part of the ongoing plan to systematically review drugs represented on the BCF and ECF, the Committee periodically reviews recommendations for changes to the BCF and ECF, which will also assist with electronic prescribing. The Committee previously reviewed changes to the BCF at the November 2008 DoD P&T Committee meeting. Further information will be presented at an upcoming meeting for recommendations for changes to the ECF; no action necessary.

10) ADJOURNMENT

The meeting adjourned at 1700 hours on 18 February 2009. The next meeting will be 13–14 May 2009.

Appendix A – Attendance
Appendix B – Table of Medical Necessity Criteria
Appendix C – Implementation Status of UF Recommendations/Decisions
Appendix D – Table of Abbreviations

SUBMITTED BY:

COL John Kugler, MC, USA
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

~~S. Ward Casscells, III, M.D.~~
Ellen P. Embrey
(performing the Duties of
ASD/HA)

Appendix A – Attendance

Voting Members Present	
COL John Kugler, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director DoD Pharmacoeconomic Center (Recorder)
COL Ted Cieslak, MC	Army, Physician at Large
COL Peter Bulatao *for Col Carol Labadie, MSC*	Army, Pharmacy Officer, Alternate
Col Everett McAllister, BSC	Chief, Pharmaceutical Operations Directorate
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
Col Mark Butler, BSC	Consultant to the AF/SG
LTC Bruce Lovins, MC	Army, Family Practice Physician, Alternate
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician, Alternate
CDR Walter Downs, MC *for LCDR Scott Akins*	Navy, Internal Medicine Physician, Alternate
CDR David Tanen, MC	Navy, Physician at Large
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Major Jeremy King, MC	Air Force, OB/GYN Physician
Mr. Joe Canzolino	Department of Veterans Affairs
Voting Members Absent	
LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
COL Carol Labadie, MSC	Army, Pharmacy Officer
Major William Hannah, MC	Air Force, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician Alternate
Nonvoting Members Present	
CDR James Ellzy	DoD P&T Vice Chairman
Ms. Carol Cooper	Deputy General Counsel, TMA
COL Kent Maneval, MSC	Defense Medical Standardization Board
Maj Peter Trang	Defense Supply Center Philadelphia
Mr. William Davies	TMOP/TRRx Contracting Officer on Record
Nonvoting Members Absent	
Lt Col Paul Hoerner, BSC	Deputy Director, DoD Patient Safety Center

Appendix A – Attendance – (continued)

Guests	
Col Trinka Coster, MC	Pharmacovigilance Center (PVC), Army, Office of the Surgeon General
CAPT Sheri Kirshner	Fort Detrick, Defense Medical Standardization Board
LtCol Teresa Bisnett, MC	Wilford Hall Medical Center
Lt Col Don Faust	Office of the Assistant Secretary of Defense, Health Affairs
LCDR Mike Lee	Indian Health Service
Debra Khachikian, PharmD	Department of Veterans Affairs PBM
Annabel Schumacher, PharmD	Wilford Hall Medical Center
Others Present	
CDR Matthew Carlberg	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
MAJ Misty Carlson, MC	DoD Pharmacoeconomic Center
Maj Joshua Devine, BSC	DoD Pharmacy Outcomes Research Team
Shana Trice, PharmD	DoD Pharmacy Outcomes Research Team
Eugene Moore, PharmD	DoD Pharmacoeconomic Center
Angela Allerman, PharmD	DoD Pharmacoeconomic Center
David Meade, PharmD	DoD Pharmacoeconomic Center
Jeremy Briggs, PharmD	DoD Pharmacoeconomic Center
Dean Valibhai, PharmD	DoD Pharmacy Operations Center contractor
Brian Beck, PharmD	DoD Pharmacy Operations Center contractor
Roger Potyk, PharmD	DoD Pharmacy Outcomes Research Team contractor
Stephen Yarger, PhD	DoD Pharmacy Outcomes Research Team contractor
Esmond Nwokeji, PhD	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B – Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Beclomethasone HFA MDI (Qvar) Budesonide MFA MDI (Pulmicort Flexhaler) Ciclesonide HFA MDI (Alvesco) Flunisolide CFC MDI (Aerobid, Aerobid M) Triamcinolone CFC MDI (Azmacort) **Inhaled Corticosteroids (ICS)**	• Use of formulary alternatives is contraindicated • Formulary agents have resulted or are likely to result in therapeutic failure. • No alternative formulary agent is available - specifically applies to budesonide, as it is pregnancy category B.
Formoterol (Perforomist) inhalation solution **Long-Acting Beta Agonists (LABAs)**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

CFC: chlorofluorocarbon

HFA: hydrofluroalkane

MDI: metered dose inhaler

*: CFC-containing pressurized MDIs likely will cease marketing as of 31 Dec 2009

Appendix C – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Feb 09	Inhaled Corticosteroids	▪ Beclomethasone HFA MDI (Qvar) ▪ Budesonide MFA MDI (Pulmicort Flexhaler) ▪ Ciclesonide HFA MDI (Alvesco) ▪ Flunisolide CFC MDI (Aerobid, Aerobid M) ▪ Triamcinolone CFC MDI (Azmacort)	BCF	▪ Fluticasone DPI (Flovent Diskus) ▪ Fluticasone HFA MDA (Flovent HFA)	pending approval	pending approval
Feb 09	Long-Acting Beta Agonists	▪ formoterol inhalation solution (Perforomist)	BCF	▪ Salmeterol DPI (Serevent Diskus)	pending approval	pending approval
Feb 09	Inhaled Corticosteroids / Long-Acting Beta Agonist Combinations	(No ICS/LABA combinations recommended for NF placement Feb 09)	BCF	▪ Fluticasone/salmeterol DPI (Advair Diskus) ▪ Fluticasone/salmeterol HFA MDI (Advair HFA)	pending approval	pending approval
Nov 08	Short-Acting Beta Agonists	▪ albuterol chlorofluorocarbon (CFC) metered dose inhaler (MDI) (no longer manufactured) ▪ metaproterenol (Alupent) CFC MDI (no longer marketed) ▪ metaproterenol inhalation solution ▪ pirbuterol (Maxair) MDI	BCF	▪ Ventolin HFA (albuterol hydrofluoroalkane (HFA) MDI ▪ Albuterol inhalation solution; Note – does not include the following: Accuneb 0.021% [0.63 mg/mL] Accuneb 0.042% [1.25 mg/3mL] Albuterol 0.5% [2.5 mg/0.5 mL in 0.5 unit dose vial]	10 Feb 09	8 Apr 09 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Nov 08 (update to include nasal antihistamines; nasal steroids reviewed Nov 05 & Aug 07 for Veramyst)	Nasal Allergy Drugs	▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ Fluticasone propionate (generic Flonase) ▪ Azelastine (Astelin)	10 Feb 09	8 Apr 09 (60 days)
Nov 08 & Aug 08 (update; reviewed Nov 05)	Antidepressants I	**Recommended for non-formulary status Aug 08; no change to non-formulary status in Nov 08** ▪ desvenlafaxine (Pristiq)	BCF	No changes to BCF recommended Aug 08	10 Feb 09; original signing date 24 Oct 08	7 Jan 09 (60 days)
Aug 08 (update; reviewed Nov 05)	Antidepressants I	To remain NF ▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg weekly admin. (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen & special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Nov 08	ACE inhibitors – Renin Angiotensin Antihypertensives	Previously non-formulary, recommended for UF status Nov 08 ▪ ramipril (Altace generic)	BCF	▪ No changes recommended to BCF at Nov 08 meeting; ramipril removed from Non-formulary status and designated as Uniform Formulary immediately upon signing of the minutes	10 Feb 09	N/A
Oct 08 (interim teleconference meeting) & Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	24 Oct 08;; original signing date: 27 Aug 08	26 Nov 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	▪ OneTouch Ultra 2 strips (for OneTouch Ultra 2, Ultra Mini, and Ultra Smart meters) ▪ TrueTrack strips (for TrueTrack meter) ▪ Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) ▪ Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check ▪ Plus all other store/private label brand strips not included on the UF (see BCF/ECF column)	BCF	**Basic Core Formulary SMBGS test strips** ▪ Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	24 Oct 08	17 Mar 09 (120 days)
Aug 08 (**re-review;** Feb 06 original review)	Overactive Bladder (OAB) Agents	▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	24 Oct 08	4 Feb 09 (90 days)
Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	**Recommended for non-formulary status Aug 08** ▪ nisoldipine geomatrix (Sular geomatrix)	BCF	No changes to BCF recommended Aug 08	24 Oct 08	7 Jan 09 (60 days)
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR, ER (Dynacirc; Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER HS dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)		Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)		▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** ▪ Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ zileuton (Zyflo)		Currently BCF ▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** ▪ olmesartan/amlodipine (Azor)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation date: 26 Nov 08 original implementation date: 29 Oct 08 (60 days)
		To remain NF ▪ valsartan amlodipine (Exforge)		No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ Moexipril +/- HCTZ (Univasc; Uniretic) ▪ perindopril (Aceon) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) (D/C'd from market) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan+/- HCTZ (Avapro, Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- (Diovan; Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel, generics) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / noreth. 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan +/- HCTZ (Teveten; Teveten HCT) ▪ irbesartan +/-HCTZ (Avapro; Avalide) ▪ olmesartan +/- HCTZ (Benicar; Benicar HCT) ▪ valsartan +/- HCTZ (Diovan; Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	▪ selegiline transdermal patch (Emsam)	ECF	▪ phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	**Recommended for non-formulary status Nov 06:** 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)		▪ nystatin ▪ clotrimazole	17 Jan 07	18 Mar 07 (60 days)
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06 (re-classified Aug 07; and updated Jun 08; see above)	Misc Antihypertensive Agents (ACE/CCB combos now part of RAAs class)	(ACE/CCB combos now part of RAAs class) ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	(ACE/CCB combos now part of RAAs class) ▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
May 05	PDE5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary CFC = chlorofluorocarbon; ER = extended release; HFA = hydrofluoroalkane; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle; AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MDIs = metered dose inhalers; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; NADs = Nasal Allergy Drugs; OABs = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SABAs = Short-Acting Beta Agonists; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones *The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])						

Appendix D – Table of Abbreviations

AE	adverse event
AERS	Adverse Event Reporting System
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	Cost-effectiveness analysis
CFC	chlorofluorocarbon
CFR	Code of Federal Regulations
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DoD	Department of Defense
DPI	dry powder inhaler
ECF	Extended Core Formulary
EIB	exercise-induced bronchospasm
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
FSS	Federal Supply Schedule Price
FY	fiscal year
GDH-PQQ	glucose dehydrogenase pyrroloquinolinequinone
GOLD	Global Initiative for Obstructive Lung Disease
HA	Health Affairs
HFA	hydrofluoroalkane
HPA	hypothalamic-pituitary-adrenal
ICS	Inhaled Corticosteroid drug class
LABA	Long-Acting Beta Agonist drug class
ICS/LABA	Inhaled Corticosteroid / Long-Acting Beta Agonist combinations drug class
MDI	metered dose inhaler (pressurized)
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
NAD	Nasal Allergy drug class
NDAA	National Defense Authorization Act
NAEPP	National Asthma Education and Preventive Program (NAEPP)
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDC	percentage of days covered
PEC	Pharmacoeconomic Center
PEF	peak expiratory flow
PORT	Pharmaceutical Outcomes Research Team
Pulmonary I	Pulmonary I drug class
QL	quantity limit
SMBGS	self-monitored blood glucose system
TFL	TRICARE for life beneficiary
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
November 2008

1) CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 18 November 2008 and at 0730 on 19 November 2008 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2) ATTENDANCE

The attendance roster is found in Appendix A.

3) REVIEW MINUTES OF LAST TWO MEETINGS

A. Updates to the minutes — Updates to the June 2008 DoD P&T Committee meeting minutes for the reviewed drug classes' implementation dates were discussed. Implementation dates from the June 2008 meeting for the designated non-formulary drugs delayed to 26 November 2008.

B. Approval of August minutes — S. Ward Casscells, III, MD, approved the minutes of the August 2008 DoD P&T Committee meeting on 24 October 2008.

C. Interim October meeting — An interim teleconference meeting was held on 27 October 2008 to re-analyze the cost effectiveness of the triptan drug class for Uniform Formulary (UF) placement. The recommendations from the interim meeting were reviewed by CDR James Ellzy. The Committee agreed to maintain the original medical necessity (MN) criteria and implementation date (90 days; 26 November 2008). The minutes are under review by TMA.

4) REVIEW OF RECENTLY FDA APPROVED AGENTS

A. Re-review of Antidepressant-1 (AD-1) - Desvenlafaxine (Pristiq)

The committee re-reviewed the cost-effectiveness and Uniform Formulary (UF) status of desvenlafaxine (Pristiq) that was originally conducted at the August 2008 meeting. Manufacturers were offered the opportunity to re-submit Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions that exceeded the Federal Ceiling Price. A revised UF VARR was submitted for desvenlafaxine. The August 2008 DoD P&T Committee meeting minutes were originally signed by the Director, TMA on 24 October 2008.

Relative Clinical Effectiveness — The committee agree that there was no reason to repeat the review since there was no significant new information in the intervening three months. The relative clinical effectiveness of desvenlafaxine (Pristiq) was reviewed at the August 2008 meeting. Desvenlafaxine (Pristiq) is a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) that is included in the Antidepressant-1 (AD-1) drug class. The AD-1 drug class was originally reviewed for UF placement in November 2005. Desvenlafaxine is an extended release (ER) formulation of the major active metabolite of venlafaxine ER (Effexor XR), and is approved solely for treating major depressive disorder in adults. Generic formulations of venlafaxine ER are

expected in 2010.

Relative Clinical Effectiveness Conclusion — At the November 2008 meeting the committee agreed to accept the conclusion from the August 2008 meeting. August 2008 P&T Committee meeting members concluded (15 for, 0 opposed, 0 abstained, 0 absent) that desvenlafaxine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other AD-1 agents currently included on the UF. A review of the literature from August 2008 to the present found no new data to alter the previous clinical conclusion.

Cost Effectiveness — A cost minimization analysis (CMA) was used to evaluate the cost effectiveness of desvenlafaxine relative to the UF AD-1s: citalopram (Celexa, generics), sertraline (Zoloft, generics), venlafaxine immediate release (Effexor, generics), venlafaxine ER (Effexor XR), and the nonformulary (NF) AD-1s bupropion ER (Wellbutrin XL, generics), and duloxetine (Cymbalta). The analysis included pricing to reflect the offered UF VARR. Results of the CMA showed that the projected weighted average daily cost of desvenlafaxine was significantly higher than the current market drug mix of AD-1 class comparators, when future market conditions were considered.

Relative Cost Effectiveness Conclusion — The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that desvenlafaxine (Pristiq) is not cost effective relative to the other AD-1s included on the UF when future market conditions were considered.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 2 opposed, 1 abstained, 0 absent) that desvenlafaxine (Pristiq) remain designated as nonformulary on the UF. This recommendation was based on the clinical effectiveness conclusion and the cost determination when future market conditions were considered. Citalopram, sertraline, venlafaxine, and venlafaxine ER (Effexor XR) remain the most cost effective AD-1 agents on the UF compared to desvenlafaxine.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** —At the November 2008 meeting the Committee agreed to maintain the original MN criteria from the August 2008 meeting. Based on the clinical evaluation of desvenlafaxine and the conditions for establishing MN of a nonformulary medication provided for in the UF rule, the P&T Committee recommended in June 2008 (June vote:14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for desvenlafaxine (Pristiq). (See Appendix B for full MN criteria.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** —At the November 2008 meeting the committee agreed not to change the original 60-day implementation period from the August 2008 meeting (August vote: of 14 for, 0 opposed, 1 abstained, 0 absent). The implementation date will be effective 07 January 2009. TMA will send a letter to beneficiaries affected by this UF decision.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

5) DRUG CLASS REVIEW — SHORT-ACTING BETA AGONISTS (SABAs)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the inhaled Short-Acting Beta Agonists (SABAs). There are four SABA products marketed in the US that are formulated as pressurized metered dose inhalers (MDIs) or solutions for inhalation: albuterol (a racemic mixture), levalbuterol (the (R)-enantiomer form of albuterol), metaproterenol, and pirbuterol. The SABA inhaled solutions include albuterol (Accuneb, generics; various concentrations), levalbuterol (Xopenex), and metaproterenol (Alupent, generics).

As of 31 December 2008, hydrofluoroalkane (HFA) will replace chlorofluorocarbon (CFC) as the propellant in albuterol MDIs. The SABA MDI formulations include albuterol HFA (Ventolin HFA, Proventil HFA, ProAir), levalbuterol HFA (Xopenex), and pirbuterol (Maxair). Generic formulations of albuterol MDI and metaproterenol CFC (Alupent) using the CFC propellant are no longer manufactured, but supplies have not yet been exhausted. The three albuterol HFA products are not considered therapeutically interchangeable by the FDA.

In the past fiscal year, over $43M was spent on the SABAs at all three points of service in the Military Health System (MHS), with $30M spent in TRICARE Pharmacy Retail Network (TRRx), $10M in the Military Treatment Facilities (MTFs), and $3M in the TRICARE Mail Order Pharmacy (TMOP). In terms of numbers of prescriptions dispensed in the MTFs, Proventil HFA is the highest utilized SABA, followed by Xopenex HFA, Ventolin HFA, and Proair HFA. In the TRRx, the top three drugs in terms of numbers of prescriptions dispensed are generic albuterol CFC MDI (but has declining usage due to dwindling stock), ProAir HFA MDI, and Xopenex HFA MDI.

Information regarding the safety, effectiveness, and clinical outcomes of the SABAs was considered by the Committee. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic

class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the pharmaceutical agents included on the UF in that therapeutic class. The clinical effectiveness review for the SABAs was limited to the outpatient setting; emergency department (ED) use was evaluated only when pertinent.

Relative Clinical Effectiveness Conclusion — The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusion:

a) In terms of efficacy/clinical effectiveness, there is little evidence to suggest there are clinically significant differences between agents for their FDA approved indications. Other conclusions regarding efficacy include the following:

- Clinical Practice Guidelines – Evidence based guidelines from the VA/DoD Clinical Practice Group, Global Initiative for Asthma, National Heart, Lung and Blood Institute/National Asthma Education & Prevention Program, and Global Initiative for Chronic Obstructive Lung Disease do not list a preference for one SABA over another for treating asthma, exercise-induced bronchospasm (EIB) or chronic obstructive pulmonary disease (COPD).
- Asthma
  - *MDI and inhalation solution administration – placebo-controlled studies*: For asthma, all the SABA agents were more efficacious than placebo at improving the change in forced expiratory volume in one second (FEV1) $\geq$ 12% from baseline, whether administered via MDI or inhalational solution.
  - *MDI administration – albuterol vs. levalbuterol*: There are no studies in adults or children assessing efficacy of albuterol vs. levalbuterol when administered by metered-dose inhaler in the outpatient setting.
  - *Inhalation administration – albuterol vs. levalbuterol in adults:* For adults with asthma, there is little evidence to suggest there are clinically relevant differences between albuterol and levalbuterol when administered via inhaled solutions (e.g., nebulized route) in either the outpatient or emergency department (ED) settings in terms of number of puffs of rescue medication used daily or hospitalization admission rates from the ED.
  - *Inhalation administration – albuterol vs. levalbuterol in children*: There are conflicting and inconclusive results as to whether there are efficacy differences between albuterol and levalbuterol inhalation solution when administered in the outpatient or ED settings to children with asthma. Some studies reported no clinically significant differences in outcomes such as changes in asthma symptom score, symptom-free days, rescue medication use, and hospitalization rates between albuterol and levalbuterol. However, levalbuterol treatment resulted in statistically significant results in terms of more asthma-controlled days, higher quality of life scores, and lower hospitalization admission rates from the

ED compared to albuterol. Interpretation of the results of these studies is complicated by the low patient enrollment, varying definitions of criteria for hospitalization, and enrollment of patients as old as 18-21 years.

- EIB – Placebo controlled trials with albuterol administered via MDI 15 to 30 minutes before exercise reported statistically significant results in terms of preventing exercise-related symptoms compared to placebo. Although levalbuterol MDI (Xopenex) is not currently approved by the FDA for EIB, the results of placebo-controlled phase III trials do not suggest that the effect of levalbuterol at preventing EIB symptoms would differ from albuterol.
- COPD - There is insufficient evidence to compare the SABAs when used in COPD.
- CFC vs. HFA efficacy - HFA products were as effective as CFC products when evaluated in head-to-head studies. Placebo-controlled trials assessing efficacy of HFA albuterol with CFC albuterol have reported similar effects on percentage change in FEV1.

b) With regards to safety/tolerability, the following conclusions were made:

- *Discontinuation rates due to adverse events (AEs)* - SABAs are associated with similar systemic adverse effects. A systematic review found no clinically relevant differences in discontinuation rates due to changes in heart rate, blood pressure, palpitations, nervousness, anxiety, tremor, hyperglycemia or hypokalemia between albuterol and levalbuterol inhalation solution.
- *Rare but serious AEs* – There do not appear to be clinically relevant differences between the SABAs in terms of serious adverse effects (e.g., paradoxical bronchospasm, cardiac effects).
- *Inhalation solution administration – albuterol vs. levalbuterol* - In the outpatient setting, in both adults and children, the incidence of the withdrawal rates due to AEs and overall AE rates were similar between albuterol and levalbuterol inhaled solutions. However, in children there is insufficient evidence from the outpatient studies to determine whether there are clinically relevant differences in the incidence of tachycardia, as conflicting results were reported. One study reported a lower incidence of tachycardia with albuterol compared to levalbuterol, while another reported that both drugs resulted in a change of heart rate of 4 beats per minute.
- *MDI administration – albuterol vs. levalbuterol* - There is insufficient data with the SABA MDI formulations to assess safety differences between albuterol and levalbuterol.
- *Drug-Drug interactions*- Drug-drug interactions between the SABAs are well-known and considered a class effect.
- *FDA Adverse Event Reporting System (AERS)* – FDA AERS data shows higher signals than expected with device malfunction/failure for Proair HFA MDI and Proventil HFA MDI. However, this is observational data only and these safety signals have not been validated.

c) With regards to differences between the SABAs in terms of other factors, the following conclusions were made:

- Special populations – The Committee recognized that the pediatric FDA-approved age ranges differ between the products. All four SABAs are labeled as category C drugs for pregnancy and breast feeding, and infant risk cannot be ruled out.
- CFC Phase out – By 31 December 2008, all albuterol CFC metered-dose inhalers will no longer be available. Metaproterenol CFC MDIs (Alupent) will also cease manufacturing by the end of 2008. It is likely that pirbuterol CFC MDIs (Maxair) will also be removed from the market.
- HFA formulations - There are only minor differences between the HFA formulations of albuterol and levalbuterol, including presence of a dose counter (Ventolin HFA is the only product with a dose counter), requirements for priming, storage conditions, and excipients (Ventolin HFA is the only SABA that does not contain alcohol). However, per FDA ruling, the HFA albuterol agents are not interchangeable.
- Delivery devices - There are no clinically relevant difference among the SABAs in terms of alternative delivery devices (MDI with a spacer/holding chamber, nebulizer, dry powder inhalers) compared with a standard MDI in stable asthma or COPD.
- Provider Survey – A survey of MTF providers found that albuterol HFA MDI was preferred over levalbuterol HFA MDI (Xopenex) in the outpatient setting for relief of bronchospasm.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

Relative Cost Effectiveness — In considering the relative cost-effectiveness of pharmaceutical agents in the SABA drug class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Cost minimization analysis (CMA) and budget impact analysis (BIA) were used to evaluate the cost effectiveness of the SABA agents.

Relative Cost Effectiveness Conclusion - Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded the following:

a) Results from the CMA of SABA MDIs revealed that Ventolin HFA was the most cost effective SABA MDI agent overall.

b) Results from the CMA of SABA inhalant solutions revealed that albuterol inhalation solution (generic; 2.5 mg/3mLconcentration) was the most cost effective agent overall.

c) The potential impact of scenarios with selected SABA agents designated formulary or nonformulary on the UF was evaluated with the BIA. Albuterol CFC

inhaler and metaproterenol inhaler were not included in the BIA as they are no longer being manufactured. BIA results designated pirbuterol (Maxair) CFC MDI and metaproterenol inhalant solution (generic) nonformulary on the UF as the most favorable scenario for the MHS.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the cost effectiveness conclusions stated above.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** — In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SABA agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 1 abstained, and 0 absent) to recommend that:

1. Albuterol HFA inhaler (Ventolin HFA, Proventil HFA, Proair HFA), levalbuterol inhaler (Xopenex HFA), albuterol inhalation solution (Accuneb, generics), and levalbuterol inhalant solution (Xopenex unit dose nebulizer solution) be classified as formulary on the UF; and
2. Pirbuterol CFC inhaler (Maxair) and metaproterenol inhalation solution (Alupent, generics) be designated as nonformulary on the UF, based on cost effectiveness.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: MN CRITERIA*** — Based on the clinical evaluation for pirbuterol inhaler (Maxair)and metaproterenol inhalation solution (Alupent, generics), and the conditions for establishing medical necessity for a nonformulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) MN criteria for pirbuterol inhaler (Maxair) and metaproterenol inhalation solution (Alupent, generics). Albuterol CFC inhaler and metaproterenol CFC inhaler (Alupent) will not be included on the MN criteria as they will not be available after 31 Dec 08. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** — The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday one week following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin the first Wednesday one week following approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION — The P&T Committee considered the BCF status of the SABA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 0 absent) to recommend that albuterol inhalant solution (generics, excludes Accuneb and the 0.5% [2.5 mg/0.5ml] unit dose vial) and the Ventolin HFA brand of albuterol HFA MDI be designated as BCF immediately on signing of the November 2008 P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: QUANTITY LIMITS - The P&T Committee updated the quantity limits (QLs) for the SABAs. The P&T Committee voted (15 for, 0 opposed, 1 abstained, and 0 absent) to recommend the QLs outlined in Appendix E.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6) DRUG CLASS REVIEW — NASAL ALLERGY DRUGS (NADs)

Relative Clinical Effectiveness — The P&T Committee evaluated the clinical effectiveness of the Nasal Allergy Drugs (NADs). The class is comprised of three subclasses as listed below. The nasal corticosteroids were previously reviewed for UF placement in November 2005 and August 2007.

- *Nasal corticosteroids*: beclomethasone (Beconase AQ), budesonide (Rhinocort AQ), ciclesonide (Omnaris), flunisolide (Nasarel, generics), fluticasone furoate (Veramyst), fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and triamcinolone (Nasacort AQ)
- *Nasal Antihistamines*: azelastine (Astelin) and olopatadine (Patanase)
- *Nasal Anticholinergics*: ipratropium (Atrovent, generics)

Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

MHS expenditures for the NAD class exceeded $63M in FY 2008 (MTF: $18.6M, TRRx $37.5M, TMOP $7M). In terms of numbers of prescriptions dispensed, generic fluticasone propionate (Flonase) is the highest utilized nasal allergy drug in the MTFs,

followed by mometasone furoate (Nasonex), and azelastine (Astelin). This utilization pattern is also seen in the TRRx.

Relative Clinical Effectiveness Conclusion — The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusion:

Nasal corticosteroids

a) With regards to efficacy/clinical effectiveness of the nasal corticosteroids, the following conclusions were made:

- FDA-approved indications – The Committee recognized that there were minor differences among the drugs with regard to FDA-approved uses for seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), prophylaxis of allergic rhinitis (AR) symptoms, nonallergic rhinitis, and nasal polyps. Additionally, the pediatric FDA-approved age ranges differ between the products.
- Clinical Practice Guidelines – Evidence-based guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) consider the nasal corticosteroids as the most effective drug class at reducing allergic rhinitis symptoms of sneezing, rhinorrhea, nasal congestion, and itching.
- Pharmacodynamic/pharmacokinetic properties – The AAAAI guidelines concluded that despite differences in topical potency, lipid solubility, receptor binding affinity, and systemic bioavailability, the overall clinical response does not appear to vary significantly between drugs.
- Efficacy for SAR/PAR – The Committee concluded there was no new data to change the previous conclusion from the 2005 meeting that there was no evidence of clinically relevant differences between beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone, and triamcinolone at relieving AR symptoms.
- Efficacy of newer agents – Fluticasone furoate (Veramyst) was non-inferior to fluticasone propionate (Flonase, generics) at relieving symptoms of SAR; there was no new data to change this conclusion. The newest nasal corticosteroid, ciclesonide (Omnaris) does not have published data comparing efficacy to other nasal corticosteroids. Placebo-controlled trials with ciclesonide report statistically significant improvements in patients with SAR and PAR.
- Relief of ocular symptoms - None of the nasal corticosteroids are FDA-approved for use in reducing ocular symptoms of itching, tearing or erythema. However, all of the agents, with the exception of ciclesonide, have shown efficacy at reducing ocular symptoms in placebo-controlled trials.
- Nasal polyps – Data from clinical trials conducted with beclomethasone, budesonide, and fluticasone propionate report reductions in the size of nasal polyps. Both mometasone furoate and beclomethasone are FDA-approved for nasal polyps.

b) With regards to regards to safety and tolerability, the following conclusions were made:

- Local effects - Nasal irritation, epistaxis, and rhinorrhea are the most common local AEs and are equally likely to occur with any of the nasal corticosteroids.
- Pharmacodynamic/pharmacokinetic properties – Minor differences in binding affinity, lipophilicity, and bioavailability between the products have not correlated to clinically relevant differences in safety. Pharmacokinetic studies report that the newer agents would be expected to pose fewer risks than the older agents (flunisolide, beclomethasone, budesonide, and triamcinolone).
- Systemic effects- For systemic effects of hypothalamic pituitary adrenal-axis suppression, growth suppression, and cataract formation, there is insufficient evidence to determine whether one nasal corticosteroid is more likely to cause these effects than another. When given in recommended doses, the nasal corticosteroids are not generally associated with clinically significant systemic adverse effects. Providers and patients must assess the risks to benefits, if higher than recommended doses are required.
- Tolerability and patient preferences - Patient preferences may play a role in differentiating between the nasal corticosteroids. However, the available clinical data is poor, and no nasal corticosteroid has proven superior to the others in patient preference trials. More well-designed head-to-head trials are needed to support superiority of a nasal corticosteroid based on tolerability and compliance.

c) With regards to differences in other factors, the following conclusions were made:

- Special populations – Budesonide (Rhinocort AQ) is the only nasal corticosteroid with a pregnancy category B rating by the FDA (low evidence of risk to humans), which was based on a retrospective review of data from three Swedish registries and one prospective study. All the nasal corticosteroids have a class labeling that these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Provider survey – A survey of MTF providers found that the majority of prescribers (49%) preferred fluticasone propionate (Flonase, generics) as their first choice of nasal corticosteroid, followed by no preference (17%), and mometasone (15%). Providers showed no preference for differences in formulations between the products (e.g., hypotonic formulation, ergonomic design, prodrug active ingredient, scent-free product, or preservative-free product).

Nasal antihistamines

a) With regards to efficacy/clinical effectiveness of the nasal antihistamines, the following conclusions were made:

- FDA-approved indications – The Committee recognized that there were minor differences between olopatadine (Patanase) and azelastine (Astelin) with

regard to FDA-approved uses for SAR and nonallergic rhinitis (e.g., vasomotor rhinitis [VMR]), and pediatric approval.

- Clinical Practice Guidelines – AAAAI guidelines state that nasal antihistamines are generally less effective than nasal corticosteroids for treating AR, but may be considered for use as first-line treatment for AR and nonallergic rhinitis. Nasal antihistamines are associated with a clinically significant effect on nasal congestion.
- Efficacy for SAR – Both nasal antihistamines are superior to placebo in relieving symptoms of SAR. Determining whether there are relevant clinical differences in efficacy between olopatadine and azelastine is difficult because different rating scores were used in the individual placebo-controlled trials.
- Efficacy for VMR: Only azelastine is FDA-approved for treating the symptoms of VMR, which consist of postnasal drip, sneezing, rhinorrhea, and nasal congestion. FDA-approval was based on the results of two placebo-controlled studies in 200 patients that used a rating scale not previously seen in the literature.
- Head to head study- The one head-to-head trial comparing the use of olopatadine with azelastine was conducted in an allergan exposure unit, making applicability to the clinical setting difficult.

b) With regards to safety and tolerability of the nasal antihistamines, the following conclusions were made:

- Local adverse effects: package insert data- For safety data, package insert data report a higher incidence of bitter taste and somnolence with azelastine, while olopatadine has a higher incidence of epistaxis.
- Local adverse effects: AAAAI guidelines – the AAAAI guidelines recognize that the two nasal antihistamines can cause sedation and can inhibit skin test reactions, due to systemic absorption.
- Patient preferences and tolerability – There is insufficient evidence to determine whether clinically relevant differences exist between the nasal antihistamines with respect to patient preferences and tolerability. The available clinical data is sparse, and is limited to manufacturer-sponsored studies that are not yet available in peer-reviewed publications.

c) With regards to other factors,

- Provider survey - A survey of MTF providers found that 37% of responders preferred a nasal corticosteroid over a nasal antihistamine for managing AR and nonallergic rhinitis.
- Onset and duration of action – The Committee recognized that the onset of action to relieve AR symptoms was slightly faster with olopatadine compared to the package insert data for azelastine (0.5 - 1 hour vs. 2-3 hours). However, the onset of action with both nasal antihistamines is faster than that reported overall with nasal corticosteroids (2-3 days).

Nasal anticholinergic agents

a) With regards to efficacy/clinical effectiveness, safety, tolerability and other factors of the ipratropium nasal spray (Atrovent, generics), the following conclusions were made:

- FDA-approved indications – Ipratropium is solely indicated for the relief of SAR in adults and children 12 years of age and older.
- Clinical Practice Guidelines – AAAAI guidelines state that nasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. Although AEs are minimal, dryness of the nasal membranes may occur.
- Efficacy - Further head-to-head trials are needed to prove the superiority of a nasal anticholinergic over a nasal antihistamine or nasal corticosteroid in the treatment of rhinorrhea.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

Relative Cost Effectiveness – In considering the relative cost-effectiveness of pharmaceutical agents in the NAD drug class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited, to sources of information listed in 32 CFR 199.21(e)(2). CMA and BIA were used to evaluate the cost effectiveness of the NAD agents.

Relative Cost Effectiveness Conclusion — Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

a) Results from the CMA of nasal corticosteroid agents revealed that flunisolide was the most cost effective nasal corticosteroid agent overall.

b) Results from the CMA of nasal antihistamines agents revealed that azelastine was the most cost effective nasal antihistamine agent overall.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the cost effectiveness conclusions stated above.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** — In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NADs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 1 abstained, and 0 absent) to recommend that:

1) Fluticasone propionate (Flonase, generics), flunisolide (Nasarel generics), mometasone (Nasonex), azelastine (Astelin), and ipratropium nasal spray (Atrovent, generics) be classified as formulary on the UF.

2) Beclomethasone dipropionate (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), olopatadine HCl (Patanase), and triamcinolone acetonide (Nasacort AQ) be designated as nonformulary under the UF, based on cost effectiveness.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA — Based on the clinical evaluation for Beclomethasone dipropionate (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), olopatadine HCl (Patanase), triamcinolone acetonide (Nasacort AQ), and the conditions for establishing medical necessity for a nonformulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) MN criteria for beclomethasone dipropionate (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), olopatadine HCl (Patanase), and triamcinolone acetonide (Nasacort AQ). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD — The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week following a 60-day implementation period in the TMOP and TRRx, and in the MTFs, no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin the first Wednesday one week following the approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION — The P&T Committee considered the BCF status of the NADs. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (9 for, 5 opposed, 1 abstained, and 1 absent) to recommend that fluticasone propionate (Flonase, generics) and azelastine (Astelin) be designated as BCF immediately on signing of the November 2008 P&T Committee minutes by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7) UTILIZATION MANAGEMENT — PRIOR AUTHORIZATIONS (PA)/ Quantity Limits (QL) / MEDICAL NECESSITY (MN)

A. Serotonin subtype 3 receptor-blocking agents – QLs

Palonosetron capsules (Aloxi) – The serotonin subtype 3 receptor-blocking agent (5-HT3 antagonist) palonosetron was previously available only in an intravenous solution. The antiemetic is now approved as a 0.5 mg capsule for the prevention of chemotherapy induced nausea and vomiting (CINV) associated with initial and repeat courses of chemotherapy. It is administered as one capsule one hour prior to moderately emetogenic chemotherapy. There is no published data to support the chronic continuous use of palonosetron for prevention of nausea and vomiting. Palonosetron has the longest half-life of the 5-HT3 antagonists (37 - 48 hours), vs. 4-5 hours with ondansetron, 8 hours with oral granisetron, and 9-11 hours with dolasetron. Quantity limits apply to the other 5-HT3 receptor antagonists. The Committee recommended a QL of 1 capsule per fill in both the TRRx and TMOP, due to the long half-life and limited FDA-approved indication for palonosetron (solely for prevention of CINV). A new prescription would be required for each course of chemotherapy.

Granisetron transdermal (Sancuso) – Granisetron is now available in a new transdermal formulation, in addition to tablets (Kytril, generics) and an oral solution. The transdermal system is approved for the prevention of CINV for patients receiving moderately to highly emetogenic chemotherapy regimens. Granisetron is available as a 34.3 mg patch that delivers 3.1 mg per 24 hours for up to 7 days. It is applied as a single patch to the arm 24 hours prior to receiving chemotherapy, and removed 24 hours after completion of chemotherapy; it can be worn for up to 7 days, depending on the duration of chemotherapy. The Committee recommended a QL of 1 patch per fill in both the TRRx and TMOP, due to the long duration of action and limited FDA-approved indication for granisetron transdermal system (solely for prevention of CINV). A new prescription would be required for each course of chemotherapy.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to recommend quantity limits for palonosetron of 1 capsule per prescription fill in the TMOP and TRRx, and for granisetron transdermal system of 1 patch per prescription fill in the TMOP and TRRx.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Ciclesonide oral inhaler (Alvesco) – QL: Ciclesonide is an oral inhaled corticosteroid approved for the treatment of asthma in patients 12 year of age and older. It is dosed twice daily. There are existing QLs for the other oral inhaled corticosteroids. The Committee recommended QLs for ciclesonide, consistent with the limits imposed on other inhaled corticosteroids in the class.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to recommend QLs for ciclesonide oral inhaler of 2 inhalers per 30 days in the TRRx, and 6 inhalers per 90 days in the TMOP.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8) STATUS OF RAMIPRIL ON THE UF

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs and utilization trends to determine whether the UF status of agents designated as non-formulary needs to be readdressed. The P&T Committee reevaluated the UF status of ramipril (Altace, generics) in light of recent price reductions in the generic formulations across all three points of service.

Clinical Effectiveness Conclusion — The angiotensin converting enzyme (ACE) inhibitors were evaluated for UF status at the August 2005 meeting. At that meeting, the Committee concluded, in general, that ramipril had similar clinical effectiveness relative to other ACE inhibitors in regards to efficacy for treating hypertension, safety, and tolerability. The P&T Committee recognized that there were differences in clinical outcomes for myocardial infarction, heart failure, diabetic nephropathy, and patients at high cardiovascular risk.

Cost Effectiveness Conclusion — The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) that ramipril has similar cost effectiveness relative to the other UF ACE inhibitors.

COMMITTEE ACTION: UF DECISION — Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional

judgment, voted (15 for, 0 opposed, 1 abstained, and 0 absent) that ramipril be immediately reclassified as generic on the UF. Ramipril was included on the "list of non-formulary drugs for re-evaluation of UF status" presented to the BAP in January 2008 and approved by the Director, TMA on 13 February 2008. As such, no further approval is needed.

9) BASIC CORE FORMULARY / EXTENDED CORE FORMULARIES (ECF) ISSUES

The Committee was briefed at the August 2008 meeting on the efforts to implement electronic prescribing in the MHS. As part of the ongoing plan to systematically review drugs represented on the BCF/ECF, the Committee periodically reviews recommendations for changes to the BCF/ECF. At this meeting, the BCF was reviewed, as greater specificity in the drug listings is required to assist with e-prescribing efforts. Several BCF deletions were recommended by the Committee, due to such factors as low MHS utilization, therapeutic duplication, change in prescribing patterns (e.g., newer therapies causing existing drugs to be outdated), availability of generic formulations, and VA/DoD joint contracts. Appendix F outlines those drugs recommended for deletion from the BCF.

COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 0 absent) to recommend the BCF deletions as outlined in Appendix F.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

10) ITEMS FOR INFORMATION

A. Outcomes Research Reports — The Pharmacy Outcomes Research Team (PORT) reported on the status of two large outcomes studies that focused on the effects of UF changes to DoD beneficiaries and are currently underway in conjunction with the MHS Scientific Advisory Panel (SAP).

1) *Hypertension/Diabetes* — The study focuses on hypertension management among DoD beneficiaries with diabetes. One arm is designed to assess the effect of the February 2006 formulary changes in the ACE inhibitor class (i.e., classification of moexipril, moexipril/hydrochlorothiazide (HCTZ), perindopril, quinapril, quinapril/HCTZ, and ramipril as Tier 3 [nonformulary] under the UF) on blood pressure control among DoD beneficiaries receiving care at MTFs. In late October 2008, medical record abstraction for this arm was approximately 81% complete. The study will also assess cardiovascular event and procedure rates among beneficiaries who were receiving Tier 3 (nonformulary) ACE inhibitors before February 2006 and were affected by changes in the formulary status of these agents in comparison to those who were receiving formulary ACE inhibitors. Results of the study will be reported to the DoD P&T Committee in FY09.

2) *Proton Pump Inhibitor (PPI)* — The study assesses the effect of the step therapy/prior authorization program instituted in the PPI class on 24 October 2007. The UF changes placed lansoprazole (Prevacid), omeprazole/sodium bicarbonate (Zegerid) pantoprazole (Protonix), and rabeprazole (Aciphex) in Tier 3 of the UF, with generic omeprazole and branded esomeprazole (Nexium) both available at a $3 copay in TRRx and TMOP. Beneficiaries presenting prescriptions at the retail and mail order points of service for nonformulary (Tier 3) PPIs who had not received a PPI prescription in the last 180 days (new users) were required to first try omeprazole or Nexium or meet MN criteria.

   The study will assess effects of the step therapy/prior authorization program on clinical outcomes (e.g., occurrence of serious gastrointestinal (GI) events) among TRICARE for Life (TFL) beneficiaries (age 65 and older) who were new users of omeprazole or Nexium (and would not have encountered a step therapy rejection) vs. those who were new users of PPIs subject to the step therapy/prior authorization program. The analysis plan for the study is currently under development; final results are expected in FY10.

B. Joint Forces Pharmacy Seminar – LTC Spridgen gave an abridged version of the PEC plenary presentation given at the 2008 Joint Forces Pharmacy Seminar. She highlighted the trends in MHS spending and utilization of the pharmacy benefit. Also identified were trends in MTF formulary management that resulted in significant cost avoidance at the individual points of service (MTF, TMOP, TRRX).

C. National Defense Authorization Act (NDAA) Section 703 Inclusion of TRICARE Retail Pharmacy Program In Federal Procurement Of Pharmaceuticals Update - CAPT Blanche updated the committee on the litigation and status of the final rule that will implement Section 703 of the 2008 NDAA. With regards to the current litigation, the judge had not rendered a decision. The final rule is at the Office of Management and Budget (OMB). Key members from the TMA Pharmacy Operations Department and Office of General Council have met with OMB personnel. The time table for approval and the impact on the DoD P&T process are not known.

11) UF DRUG CLASS OVERVIEWS

The drug class overviews for the Pulmonary I drug class (comprised of the long-acting beta agonists, inhaled corticosteroids, and combination long-acting beta agonists/inhaled corticosteroids), Antilipidemic-Is (statins, ezetimibe, niacin, and combination products) and Fluoroquinolones were presented to the P&T Committee. The Committee provided the PEC with expert opinion regarding those clinical outcomes considered most important to use in completing the clinical effectiveness review and developing appropriate cost effectiveness models. The clinical and economic analyses of this drug class will be completed at upcoming DoD P&T Committee meetings.

12) ADJOURNMENT

The second day of the meeting adjourned at 1100 hours on 19 November 2008. The next meeting will be 18-19 February 2009.

Appendix A – Attendance
Appendix B – Table of Medical Necessity Criteria
Appendix C – Implementation Status of UF Recommendations/Decisions
Appendix D – Table of Abbreviations
Appendix E – Quantity Limit Criteria - SABAs
Appendix F – Basic Core Formulary Deletions

SUBMITTED BY:

Col John Kugler, MC
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

2 Feb-09

S. Ward Casscells, III, M.D.

Appendix A – Attendance

Voting Members Present	
COL John Kugler, MC	DoD P&T Committee Chair
LTC Stacia Spridgen, MSC	Director DoD Pharmacoeconomic Center (Recorder)
COL Ted Cieslak, MC	Army, Physician at Large
COL Peter Bulatao *for Col Isiah Harper, MSC*	Army, Pharmacy Officer, Alternate
CAPT Bill Blanche, MSC	Chief, Pharmaceutical Operations Directorate
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
CAPT Vernon Lew	Coast Guard, Pharmacy Officer
Col Mark Butler, BSC	Consultant to the AF/SG
LTC Michael Wynn *for LTC Bruce Lovins*	Army, Family Practice Physician, Alternate
LTC Jack Lewi *for COL Doreen Lounsbery*	Army, Internal Medicine Physician, Alternate
CDR Walter Downs, MC *for LCDR Scott Akins*	Navy, Internal Medicine Physician, Alternate
CDR David Tanen, MC	Navy, Physician at Large
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Ron Garcia	Navy, Internal Medicine Physician
Major Jeremy King, MC	Air Force, OB/GYN Physician
Mr. Joe Canzolino	Department of Veterans Affairs
Voting Members Absent	
LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
COL Isiah Harper, MS	Army, Pharmacy Officer
Major William Hannah, MC	Air Force, Internal Medicine Physician
LTC Bruce Lovins, MC	Army, Family Practice Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician Alternate
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
Nonvoting Members Present	
CDR James Ellzy	DoD P&T Vice Chairman
Lt Col Paul Hoerner	Deputy Director, DoD Patient Safety Center
Ms. Carol Cooper	Deputy General Counsel, TMA
Nonvoting Members Absent	
COL Kent Maneval, MS	Defense Medical Standardization Board
LCDR Thomas Jenkins	TMA Aurora
Maj Peter Trang	Defense Supply Center Philadelphia

Appendix A – Attendance – (continued)

Guests	
LT Joe Bryant	Indian Health Service
Mr. Tom Emmendorfer	Department of Veterans Affairs PBM
Ms. Brenna Mann	University of Texas Pharmacy Student
Others Present	
CDR Matthew Carlberg	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC	DoD Pharmacoeconomic Center
MAJ Misty Carlson, MC	DoD Pharmacoeconomic Center
Maj Joshua Devine, BSC	DoD Pharmacoeconomic Center
LCDR Joe Lawrence	DoD Pharmacoeconomic Center
Dr. Shana Trice	DoD Pharmacoeconomic Center
Dr. Eugene Moore	DoD Pharmacoeconomic Center
Dr. Angela Allerman	DoD Pharmacoeconomic Center
Dr. David Meade	DoD Pharmacoeconomic Center
Dr. Harsha Mistry	DoD Pharmacoeconomic Center
Dr. Jeremy Briggs	DoD Pharmacy Operations Center contractor
Dr. Stephen Yarger	DoD Pharmacy Outcomes Research Team contractor
Dr. Esmond Nwokeji	DoD Pharmacy Outcomes Research Team contractor
Ms. Deborah Garcia	DoD Pharmacy Outcomes Research Team contractor

Appendix B – Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Olopatadine (Patanase) Beclomethasone (Beconase AQ) Budesonide (Rhinocort Aqua) Ciclesonide (Omnaris) Fluticasone furoate (Veramyst) Triamcinolone (Nasacort AQ) **Nasal Allergy Drugs**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure.
Pirbuterol CFC* MDI (Maxair) Metaproterenol inhalation solution **Short-Acting Beta Agonists**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • The patient previously responded to nonformulary agent and changing to a formulary agent would incur unacceptable risk.
Desvenlafaxine (Pristiq) **(Antidepressant-1s)**	• The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

CFC: chlorofluorocarbon

MDI: metered dose inhaler

*: CFC-containing pressurized MDIs likely will cease marketing as of 31 Dec 2008

Appendix C – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Nov 08	Short-Acting Beta Agonists	▪ albuterol chlorofluorocarbon (CFC) metered dose inhaler (MDI) (no longer manufactured) ▪ metaproterenol (Alupent) CFC MDI (no longer marketed) ▪ metaproterenol inhalation solution ▪ pirbuterol (Maxair) MDI	BCF	▪ Ventolin HFA (albuterol hydrofluoroalkane (HFA) MDI ▪ Albuterol inhalation solution; Note – does not include the following: Accuneb 0.021% [0.63 mg/mL] Accuneb 0.042% [1.25 mg/3mL] Albuterol 0.5% [2.5 mg/0.5 mL in 0.5 unit dose vial]	pending approval	pending approval
Nov 08 (update to include nasal antihistamines; nasal steroids reviewed Nov 05 & Aug 07 for Veramyst)	Nasal Allergy Drugs	▪ olopatadine (Patanase) ▪ ciclesonide (Omnaris) ▪ fluticasone furoate (Veramyst) ▪ beclomethasone (Beconase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ Fluticasone propionate (generic Flonase) ▪ Azelastine (Astelin)	pending approval	pending approval
Nov 08 & Aug 08 (update; reviewed Nov 05)	Antidepressants I	**Recommended for non-formulary status Aug 08; no change to non-formulary status in Nov 08** ▪ desvenlafaxine (Pristiq)	BCF	No changes to BCF recommended Aug 08	Nov 08: pending approval; original signing date 24 Oct 08	26 Nov 08 (60 days)
Aug 08 (update; reviewed Nov 05)	Antidepressants I	To remain NF ▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg weekly admin. (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen & special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Nov 08	ACE inhibitors – Renin Angiotensin Antihypertensives	Previously non-formulary, recommended for UF status Nov 08 ▪ ramipril (Altace generic)	BCF	▪ No changes recommended to BCF at Nov 08 meeting; ramipril removed from Non-formulary status and designated as Uniform Formulary immediately upon signing of the minutes	pending approval	N/A

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Oct 08 (interim teleconference meeting) & Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	Nov 08 meeting pending approval: ; original signing date: 27 Aug 08	26 Nov 08 (90 days)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	▪ One Touch Ultra 2 strips (for One Touch Ultra 2, Ultra Mini, and Ultra Smart meters) ▪ TrueTrack strips (for TrueTrack meter) ▪ Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) ▪ Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check ▪ Plus all other store/private label brand strips not included on the UF (see BCF/ECF column)	BCF	**Basic Core Formulary SMBGS test strips** ▪ Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	24 Oct 08	17 Mar 09 (120 days)
Aug 08 (re-review; Feb 06 original review)	Overactive Bladder (OAB) Agents	▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	24 Oct 08	4 Feb 09 (90 days)
Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	**Recommended for non-formulary status Aug 08** ▪ nisoldipine geomatrix (Sular geomatrix)	BCF	No changes to BCF recommended Aug 08	24 Oct 08	7 Jan 09 (60 days)
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To Remain Non-Formulary ▪ isradipine IR, ER (Dynacirc; Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER HS dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	Revised implementation da 26 Nov 08 original implementation da 29 Oct 08 (60 days)
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)		Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation da 26 Nov 08 original implementation da 29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation da 26 Nov 08 original implementation da 29 Oct 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To remain NF • desloratadine (Clarinex) • desloratadine/pseudoephedrine (Clarinex D)		• MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** • Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	Revised implementation da 26 Nov 08 original implementation da 29 Oct 08 (60 days)
		To remain NF • zileuton (Zyflo)		Currently BCF • montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews • ACE inhibitors: Aug 05 • Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 • ARBs: May 07 • Renin inhibitors. Aug 07 • CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** • olmesartan/amlodipine (Azor)	BCF	No change to BCF recommended Jun 08	27 Aug 08	Revised implementation da 26 Nov 08 original implementation da 29 Oct 08 (60 days)
		To remain NF • valsartan amlodipine (Exforge)		No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors • Moexipril +/- HCTZ (Univasc; Uniretic) • perindopril (Aceon) • ramipril (Altace) ACE/CCB combos • felodipine/enalapril (Lexxel) (D/C'd from market) • verapamil/trandolapril (Tarka) ARBs • eprosartan +/- HCTZ (Teveten; Teveten HCT) • irbesartan+/- HCTZ (Avapro, Avalide) • olmesartan +/- HCTZ (Benicar; Benicar HCT) • valsartan +/- (Diovan; Diovan HCT)		Currently on the BCF ACE inhibitors • captopril • lisinopril • lisinopril / HCTZ ACE/CCB combos • amlodipine/benazepril (Lotrel, generics) ARBs • telmisartan (Micardis) • telmisartan HCTZ (Micardis HCT)	ACE inhibitors • 13 Oct 05 ACE/CCB combos • 26 Apr 06 ARBs • 24 July 07	ACE inhibitors • 15 Feb 06 ACE/CCB combos • 26 Jul 06 ARBs • 21 Nov 07
Nov 07	Targeted Immunomodulatory Biologics	• etanercept (Enbrel) • anakinra (Kineret)	ECF	• adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	• tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	• terazosin tablets or capsules • alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (implementation period)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / noreth. 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07 re-review (Feb 05 original)	ARBs	• eprosartan +/- HCTZ (Teveten; Teveten HCT) • irbesartan +/-HCTZ (Avapro; Avalide) • olmesartan +/- HCTZ (Benicar; Benicar HCT) • valsartan +/- HCTZ (Diovan; Diovan HCT)	BCF	• telmisartan (Micardis) • telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)
May 07	5-Alpha Reductase Inhibitors	• dutasteride (Avodart)	BCF	• finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	• zolpidem ER (Ambien CR) • zaleplon (Sonata) • ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	• zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	• selegiline transdermal patch (Emsam)	ECF	• phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	• tramadol ER (Ultram ER)	BCF	• morphine sulfate IR 15 mg, 30 mg • morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg • oxycodone/APAP 5/325 mg • hydrocodone/APAP 5/500 mg • codeine/APAP 30/300 mg • codeine/APAP elixir 12/120 mg/5 mL • tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	• travoprost (Travatan, Travatan Z) • timolol maleate for once daily dosing (Istalol) • timolol hemihydrate (Betimol) • brinzolamide (Azopt)	BCF	• latanoprost (Xalatan) • brimonidine (Alphagan P); excludes 0.1% • timolol maleate • timolol maleate gel-forming solution • pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	• temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	**Recommended for non-formulary status Nov 06:** 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)		▪ nystatin ▪ clotrimazole	17 Jan 07	18 Mar 07 (60 days)
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06 (re-classified Aug 07; and updated Jun 08; see above)	Misc Antihypertensive Agents (ACE/CCB combos now part of RAAs class)	(ACE/CCB combos now part of RAAs class) ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	(ACE/CCB combos now part of RAAs class) ▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
May 05	PDE5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
CFC = chlorofluorocarbon; ER = extended release; HFA = hydrofluoroalkane; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle;
AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MDIs = metered dose inhalers; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; NADs = Nasal Allergy Drugs; OAB = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SABAs = Short-Acting Beta Agonists; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones
*The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix D – Table of Abbreviations

5-HT3	Serotonin subtype 3 receptor-blocking agents (5-HT3 antagonists)
ACE I / RAAs	Angiotensin Converting Enzyme Inhibitor / Renin Angiotensin Antihypertensive drug class
AD-1	Antidepressant-1 drug class
AE	adverse event
AERS	Adverse Event Reporting System
AAAAI	American Academy of Allergy, Asthma and Immunology
AR	allergic rhinitis
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
CEA	cost effectiveness analysis
CFC	chlorofluorocarbon
CFR	Code of Federal Regulations
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
COPD	chronic obstructive pulmonary disease
DoD	Department of Defense
ED	emergency department
EIB	exercise-induced bronchospasm
ER	Extended release
ESI	Express Scripts, Inc
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
FSS	Federal Supply Schedule Price
FY	fiscal year
HA	Health Affairs
HCTZ	hydrochlorothiazide
HFA	hydrofluoroalkane
IR	immediate release
LIP-1	Antilipidemic-1 drug class
MDI	metered dose inhaler (pressurized)
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
NAD	Nasal Allergy drug class
NDAA	National Defense Authorization Act
OMB	Office of Management and Budget
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	Perennial allergic rhinitis
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
PPI	Proton Pump Inhibitor
QD	once daily
QL	quantity limit
SABAs	Short-Acting Beta Agonist drug class
SAR	Seasonal allergic rhinitis
SNRI	Serotonin Norepinephrine Reuptake Inhibitor

Appendix D – Table of Abbreviations (continued)

TFL	TRICARE for life beneficiary
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy Network
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refunds
VMR	vasomotor rhinitis

Appendix E – Table of Short-Acting Beta Agonists Quantity Limits

Drug	TMOP QL	TRRx QL
Current Quantity Limits		
Albuterol (AccuNeb; generic) soln 0.63mg/3mL & 1.25 mg/3mL	1650 mL per 90 days (550 unit-dose vials)	600 mL per 30 days (200 unit-dose vials)
Albuterol (generic) soln 0.083% 2.5 mg/3 mL	1650 mL per 90 days (550 unit-dose vials)	600 mL per 30 days (200 unit-dose vials)
Albuterol (generic) soln 0.5% 2.5 mg/0.5 mL (20 mL)	180 mL per 90 days (9 bottles)	60 mL per 30 days (3 bottles)
Levalbuterol (Xopenex) soln 0.63 mg/3 mL & 1.25 mg/3 mL	1080 mL per 90 days (360 unit-dose vials)	360 mL per 30 days (120 unit-dose vials)
Albuterol CFC (generic) 90 mcg MDI	102 gm per 90 days (17 gm MDI: 6 inhalers)	34 gm per 30 days (17 gm MDI: 2 inhalers)
Proposed Quantity Limits (in addition to current QLs)		
Levalbuterol (Xopenex) soln 0.31 mg/3 mL	1080 mL per 90 days (360 unit-dose vials)	360 mL per 30 days (120 unit-dose vials)
Levalbuterol HFA (Xopenex) 45 mcg MDI (8.4 gm MDI)	50.4 gm per 90 days (8.4 gm MDI: 6 inhalers)	16.8 gm per 30 days (8.4 gm MDI: 2 inhalers)
Levalbuterol HFA (Xopenex) 45 mcg MDI (15 gm MDI)	90 gm per 90 days (15 gm MDI: 6 inhalers)	30 gm per 30 days (15 gm MDI: 2 inhalers)
Albuterol HFA (Ventolin HFA) 90 mcg MDI	108 gm per 90 days (18 gm MDI: 6 inhalers)	36 gm per 30 days (18 gm MDI: 2 inhalers)
Albuterol HFA (Proventil HFA) 90 mcg MDI	40.2 gm per 90 days (6.7 gm MDI: 6 inhalers)	13.4 gm per 30 days (6.7 gm MDI: 2 inhalers)
Albuterol HFA (ProAir HFA) 90 mcg MDI	51 gm per 90 days (8.5 gm MDI: 6 inhalers)	17 gm per 30 days (8.5 gm MDI: 2 inhalers)

CFC: chlorofluorocarbon
HFA: hydrofluoroalkane
MDI: metered dose inhaler
Soln: solution

Appendix F – Basic Core Formulary Deletions

Therapeutic Category	Generic Name	Dosage	Dosage Form
ALDOSTERONE ANTAGONISTS	SPIRONOLACTONE	100MG	TABS
	SPIRONOLACTONE	50MG	
ANTIARTHRITICS	NAPROXEN	375MG	TABS
ANTICONVULSANTS	PHENYTOIN SODIUM	30MG	CAPS
	CARBAMAZEPINE	100MG	CP12
	CARBAMAZEPINE	200MG	
	CARBAMAZEPINE	300MG	
	GABAPENTIN	250MG/5ML	SOLN
	GABAPENTIN	100MG	TABS
	GABAPENTIN	400MG	
ANTIHISTAMINES	HYDROXYZINE PAMOATE	100MG	CAPS
	HYDROXYZINE PAMOATE	25MG	
	HYDROXYZINE PAMOATE	50MG	
	PROMETHAZINE HCl	12.5MG	TABS
	PROMETHAZINE HCl	50MG	
ANTINAUSEANTS	PROMETHAZINE HCl	50MG	SUPP
	METOCLOPRAMIDE HCl	5MG	TABS
ANTIPARASITICS	METRONIDAZOLE	375MG	CAPS
ANTIPARKINSON	AMANTADINE HCl	100MG	TABS
	TRIHEXYPHENIDYL HCl	5MG	
ANTI-ULCER PREPS/GASTROINTESTINAL PREPS	RANITIDINE HCl	300MG	TABS
ATARACTICS-TRANQUILIZERS	BUSPIRONE HCl	30MG	TABS
	BUSPIRONE HCl	7.5MG	
BRONCHIAL DILATORS	ALBUTEROL SULFATE	0.5% in unit dose (2.5 mg/0.5 mL)	NEBU
CEPHALOSPORINS	CEPHALEXIN MONOHYDRATE	250MG	TABS
	CEPHALEXIN MONOHYDRATE	500MG	
CNS STIMULANTS	METHYLPHENIDATE HCl	20MG	TABS
DIURETICS	HYDROCHLOROTHIAZIDE; TRIAMTERENE	25MG; 37.5MG	CAPS
	HYDROCHLOROTHIAZIDE; TRIAMTERENE	25MG; 50MG	
	CHLORTHALIDONE	100MG	TABS
	HYDROCHLOROTHIAZIDE	12.5MG	
	CHLORTHALIDONE	15MG	
	FUROSEMIDE	80MG	
ELECTROLYTES & MISCELLANEOUS NUTRIENTS	POTASSIUM CHLORIDE	8MEQ	CPCR
	POTASSIUM CHLORIDE	20%	LIQD
	POTASSIUM CHLORIDE	25MEQ	PACK
	POTASSIUM CHLORIDE	10MEQ	TBCR
	POTASSIUM CHLORIDE	8MEQ	
ERYTHROMYCINS	ERYTHROMYCIN	250MG	CPEP
	ERYTHROMYCIN ETHYLSUCCINATE	400MG/5ML	SUSP
	AZITHROMYCIN	200MG/5ML	SUSR
	ERYTHROMYCIN ETHYLSUCCINATE	400MG/5ML	
	ERYTHROMYCIN	250MG	TABS

Therapeutic Category	Generic Name	Dosage	Dosage Form
ERYTHROMYCINS	ERYTHROMYCIN ETHYLSUCCINATE	400MG	
	ERYTHROMYCIN ERYTHROMYCIN STEARATE	500MG	
	AZITHROMYCIN	600MG	
	ERYTHROMYCIN	333MG	TBEC
	ERYTHROMYCIN	500MG	
ESTROGENS	ESTROGENS, CONJUGATED	0.9MG	TABS
FUNGICIDES	NYSTATIN	500000UNIT	TABS
GLUCOCORTICOIDS	FLUTICASONE PROPIONATE	50MCG/BLIST	AEPB
	PREDNISONE	5MG/ML	CONC
	BUDESONIDE	180MCG/ACT	INHA
	BUDESONIDE	90MCG/ACT	
	PREDNISONE	2.5MG	TABS
	PREDNISONE	50MG	
MUSCLE RELAXANTS	CYCLOBENZAPRINE HCl	5MG	TABS
	METHOCARBAMOL	750MG	TABS
NON-NARCOTIC ANALGESICS	ACETAMINOPHEN; BUTALBITAL; CAFFEINE	325MG; 50MG; 40MG	CAPS
	SUMATRIPTAN SUCCINATE	4MG/0.5ML	KIT
OPHTHALMIC PREPARATIONS	PILOCARPINE HCl	3%	SOLN
	PILOCARPINE HCl	6%	
OTHER ANTIBIOTICS	ERYTHROMYCIN	2%	OINT
	CIPROFLOXACIN	500MG/5ML	SUSR
OTHER CARDIOVASCULAR PREPS	VERAPAMIL HCl	120MG	CP24
	VERAPAMIL HCl	180MG	
	VERAPAMIL HCl	240MG	
	VERAPAMIL HCl	360MG	
	AMIODARONE HCL	100MG	TABS
	AMIODARONE HCL	400MG	
OTHER HYPOTENSIVES	HYDRALAZINE HCl	100MG	TABS
PENICILLINS	AMOXICILLIN; CLAVULANIC ACID	200MG; 28.5MG	CHEW
	AMOXICILLIN; CLAVULANIC ACID	400MG; 57MG	
	AMOXICILLIN	875MG	TABS
PSYCHOSTIMULANTS-ANTIDEPRESSANTS	DOXEPIN HCl IMIPRAMINE PAMOATE	100MG	CAPS
	IMIPRAMINE PAMOATE	125MG	
	DOXEPIN HCl IMIPRAMINE PAMOATE	150MG	
	LITHIUM CARBONATE	600MG	
	NORTRIPTYLINE HCl	75MG	
	AMITRIPTYLINE HCl	100MG	TABS
	FLUOXETINE HCL	10MG	
	AMITRIPTYLINE HCl	150MG	
	FLUOXETINE HCL	20MG	
	BUPROPION HCL	200MG	TB12
TB PREPARATIONS	RIFAMPIN	150MG	CAPS
VASODILATORS CORONARY	NITROGLYCERIN	0.3MG	SUBL

Therapeutic Category	Generic Name	Dosage	Dosage Form
VASODILATORS CORONARY	NITROGLYCERIN	0.6MG	
	ISOSORBIDE DINITRATE	2.5MG	
	ISOSORBIDE DINITRATE	5MG	
XANTHINE DERIVATIVES	THEOPHYLLINE	100MG	CP24
	THEOPHYLLINE	200MG	
	THEOPHYLLINE	100MG	TB12
	THEOPHYLLINE	450MG	
	THEOPHYLLINE	600MG	TB24

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE
RECOMMENDATIONS
INTERIM MEETING
Oct 2008

DRUG CLASS REVIEW – 5-HYDROXYTRYPTAMINE AGONISTS (TRIPTANS)

The P&T Committee held an interim teleconference meeting on 27 Oct 2008 during which it re-reviewed the cost-effectiveness of the triptan drug class that was originally conducted at the June 2008 meeting. Nine voting Committee members, who constituted a majority of the entire voting Committee members, participated. All triptan drugs originally recommended for inclusion on the UF were covered by Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP). (One of the triptan drugs recommended for non-formulary status was also covered by a UF-VARR at or below the FCP, but was not considered cost-effective.) However this meeting was held because manufacturers were offered the opportunity to re-submit Uniform Formulary Voluntary Agreement for Retail Refunds submissions to include offers that would exceed the Federal Ceiling Price and to re-evaluate the clinical and cost-effectiveness of the drugs after resubmissions were received. A revised UF VARR was submitted for one drug. The 12-13 June 2008 DoD P&T Committee meeting minutes were originally signed by the Director, TMA on 27 August 2008.

Relative Clinical Effectiveness: The relative clinical effectiveness of the triptan drugs was previously reviewed at the June 2008 meeting; there were no changes to the clinical effectiveness conclusion at the interim Oct 2008 teleconference meeting. The relative clinical effectiveness review presented at the June 2008 meeting is provided below.

The P&T Committee evaluated the relative clinical effectiveness of the eight marketed 5-hydroxytryptamine agonists (triptans) in the US, almotriptan (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), sumatriptan (Imitrex), sumatriptan/naproxen (Treximet), rizatriptan (Maxalt), and zolmitriptan (Zomig). None of the triptans are available in generic formulations, although generic formulations of sumatriptan are expected in early 2009.

MHS expenditures for the triptans were approximately $70 million for the time period of May 2007 to April 2008. In terms of total quantity dispensed between May 2007 and April 2008, sumatriptan is the highest utilized triptan in the MHS (~150,000 tablets dispensed/month), followed by zolmitriptan (~60,000 tablets/month), and rizatriptan (~45,000 tablets/month). To review the full clinical effectiveness evaluation, see the Triptan DoD Drug Class Review found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion: The P&T Committee voted in June 2008 (15 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusion:

a) With regards to efficacy at providing pain relief at 2 hours,1) rizatriptan 10 mg (Maxalt) appears superior to the other triptans; 2) almotriptan (Axert), eletriptan (Relpax), sumatriptan (Imitrex) and zolmitriptan (Zomig) have comparable relative effectiveness; 3) frovatriptan (Frova) appears inferior to the other triptans, although these results are based on limited data; 4) naratriptan (Amerge) appears inferior to the other triptans; and 5) sumatriptan/naproxen (Treximet) appears superior to sumatriptan 85 mg, but there is insufficient evidence to suggest clinically relevant differences between Treximet and the other triptans.

b) With regards to other efficacy endpoints, 1) rizatriptan 10 mg (Maxalt) and almotriptan 12.5 mg (Axert) are superior to the other triptans for pain free response at 24 hours; and 2) rizatriptan 10 mg is superior to the other triptans for pain-free response at 2 hours.

c) With regards to safety and tolerability, almotriptan (Axert) and naratriptan (Amerge) had the most favorable adverse event profiles compared to the other triptans. There is only limited data for frovatriptan from the product labeling.

Relative Cost Effectiveness: The DoD P&T Committee evaluated the relative cost effectiveness of the triptans at the interim 28 October 2008 teleconference meeting. In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost Effectiveness Conclusion: The cost effectiveness of the triptan agents was evaluated by CMA, cost effectiveness analysis (CEA), and by budget impact analysis (BIA). Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (9 for, 0 opposed, 0 abstained, 0 absent) the following:

a) Results from the triptan CMA revealed that sumatriptan/naproxen (Treximet) was the most cost effective agent overall. However, sumatriptan (Imitrex) is expected to become the most cost-effective triptan when generic formulations reach the market in early 2009.

b) Results from the 2 hour pain response CEA revealed that 1) sumatriptan/naproxen (Treximet) and rizatriptan (Maxalt) are the most cost-effective agents; and 2) when the price for generic formulations of sumatriptan (Imitrex) drops below 70% of the current price, sumatriptan will become the most cost-effective agent.

c) Results from the 2 hour pain-free response CEA revealed that 1) sumatriptan/naproxen (Treximet), eletriptan (Relpax) and rizatriptan (Maxalt) are the most cost-effective agents; and 2) when the price for generic formulations of sumatriptan (Imitrex) drops below 70% of the current price, sumatriptan will become the most cost-effective agent.

d) The BIA evaluated the potential impact of scenarios with selected triptans designated formulary or non-formulary on the UF. Results from the BIA revealed that the scenario that designated almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge) as non-formulary under the UF was more favorable to the MHS.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the triptans, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (8 for, 0 opposed, 1 abstained, and 0 absent) to recommend that:

1) Sumatriptan (Imitrex), sumatriptan/naproxen (Treximet), eletriptan (Relpax), rizatriptan (Maxalt), and zolmitriptan (Zomig) be classified as formulary on the UF.

2) Almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge) be designated as non-formulary under the UF, based on cost effectiveness.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – The Committee agreed to maintain the original MN criteria from the June 2008 meeting. Based on the clinical evaluation for almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended in June (13 for, 0 opposed, 1 abstained, 1 absent) MN criteria for almotriptan, frovatriptan, and naratriptan. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – There was no change to the original 90-day implementation period from the June 2008 meeting (vote in June of 13 for, 0 opposed, 1 abstained, 1 absent). The implementation date will be effective 26 November 2008. TMA will send a letter to beneficiaries affected by this UF decision.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the triptan agents at the October interim teleconference meeting. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (8 for, 0 opposed, 1 abstained, and 0 absent) to recommend that 1) rizatriptan (Maxalt) be designated as BCF immediately upon signing of the

interim October 2008 DoD P&T Committee minutes by the Director, TMA; 2) sumatriptan (Imitrex oral tablets and one injectable sumatriptan formulation be designated as BCF when multi-source generic formulations that are cost effective reach the marketplace. As a result of the above actions, zolmitriptan (Zomig) would no longer be designated as BCF, but maintained as formulary on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: QUANTITY LIMIT (QL) RECOMMENDATIONS – There was no change to the quantity limits from the June 2008 meeting. The P&T Committee voted (13 for, 0 opposed, 1 abstained, 1 absent) to 1) to recommend QLs for sumatriptan 85 mg/naproxen 500 mg (Treximet) of 9 tablets per 30 days and 27 tablets per 90 days; 2) to recommend QLs for sumatriptan (Imitrex) 4 mg injection of 9 syringes per 30 days and 24 syringes per 90 days; and 3) to maintain the existing QLs for the other triptans.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

SUBMITTED BY:

COL John Kugler, USA, MC
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

DEC - 2 2008

S. Ward Casscells, MD

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
August 2008

1) CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 12-13 Aug 2008 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2) ATTENDANCE

The attendance roster is found in Appendix A.

3) REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – Corrections to the June 2008 DoD P&T Committee meeting minutes were tabled until the next meeting.

B. Approval of June minutes – Dr. Samuel Ward Casscells, III., M.D., will review the minutes of the June 2008 DoD P&T Committee meeting on 27 Aug 2008.

4) REVIEW OF RECENTLY APPROVED AGENTS

A. Antidepressant -1 (AD-1) – Desvenlafaxine (Pristiq)

Relative Clinical Effectiveness –Desvenlafaxine (Pristiq) is a Serotonin Norepinephrine Re-Uptake Inhibitor (SNRI) that is classified as part of the Antidepressant-1 (AD-1) drug class. The AD-1s were reviewed for Uniform Formulary (UF) placement in November 2005. Other SNRIs included on the UF are venlafaxine immediate release (Effexor, generics) and venlafaxine extended release (ER) (Effexor XR). The desvenlafaxine clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1).

Desvenlafaxine is FDA-approved for the treatment of major depressive disorder in adults. Desvenlafaxine is an extended release formulation of the major active metabolite of venlafaxine ER. Generic formulations of venlafaxine ER (Effexor XR) are expected in 2010. To review the full clinical effectiveness evaluation of desvenlafaxine, see the Desvenlafaxine New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder DoD P&T library. Note that rxnet is restricted to those with a ".mil" e-mail address.)

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that desvenlafaxine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other AD-1 agents currently included on the UF.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of desvenlafaxine (Pristiq) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the AD-1 class, particularly to the following medications: citalopram (Celexa, generics), sertraline (Zoloft, generics), venlafaxine (Effexor, generics), venlafaxine ER (Effexor XR), bupropion ER

(Wellbutrin XL), and duloxetine (Cymbalta). Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of desvenlafaxine relative to the UF AD-1s citalopram, sertraline, venlafaxine, and venlafaxine ER, and the Non-formulary (NF) AD-1s bupropion ER, and duloxetine. Results of the CMA showed that the projected weighted average daily cost of desvenlafaxine was significantly higher than its AD-1 class comparators.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that desvenlafaxine (Pristiq) is not cost effective relative to the other AD-1s included on the UF.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 0 opposed, 1 abstained, 0 absent) that desvenlafaxine (Pristiq) be designated as non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion, and the determination that citalopram (Celexa, generics), sertraline (Zoloft, generics), venlafaxine (Effexor, generics), and venlafaxine ER (Effexor XR) remain the most cost effective AD-1 agents on the UF compared to desvenlafaxine.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of desvenlafaxine and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for desvenlafaxine (Pristiq). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend: 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy Network (TRRx), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Calcium Channel Blockers (CCBs) – Nisoldipine (Sular geomatrix)

Relative Clinical Effectiveness – Nisoldipine (Sular geomatrix) is a dihydropyridine calcium channel blocker (DHP CCB) approved for treating hypertension. The CCBs were reviewed for UF placement at the August 2005 P&T Committee meeting. Other anti-hypertensive DHP CCBs included on the UF are amlodipine (Norvasc, generics), felodipine (Plendil, generics), nisoldipine coat core (Sular, generics), and nifedipine ER (Adalat CC, generics). The nisoldipine geomatrix clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1).

Nisoldipine geomatrix employs a different extended-release mechanism than the original nisoldipine product, nisoldipine coat core; both products are dosed once daily. Generic formulations of the original coat core product recently became commercially available. The geomatrix delivery system allows for a 15% lower dosage than the coat core product. To review the full clinical effectiveness evaluation of nisoldipine geomatrix, see the Nisoldipine geomatrix New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder DoD P&T library. Note that rxnet is restricted to those with a ".mil" e-mail address.)

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that there is no evidence to suggest that there are clinically relevant differences in the efficacy, safety, and clinical outcomes of nisoldipine geomatrix (Sular geomatrix) compared to nisoldipine coat core, as both products contain the same active ingredient. Additionally, the Committee agreed that nisoldipine geomatrix does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other CCB agents currently included on the UF.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of nisoldipine (Sular Geomatrix) in relation to efficacy, safety, tolerability, and clinical outcomes of other DHP CCBs, particularly to amlodipine (Norvasc, generics), felodipine (Plendil, generics) and nisoldipine (Sular coat core, generics). Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

A CMA was employed to determine the relative cost effectiveness of nisoldipine geomatrix relative to other UF DHP CCBs (nisoldipine coat core, felodipine, amlodipine). The results from the CMA revealed that the projected weighted average cost per day for therapy for nisoldipine geomatrix (Sular Geomatrix) is significantly higher than other UF CCBs amlodipine, felodipine, and nisoldipine (Sular coat core, generics).

Relative Cost Effectiveness Conclusion – P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 0 absent) that

nisoldipine geomatrix (Sular Geomatrix) is not cost effective relative to other UF DHP CCB agents.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness of nisoldipine geomatrix, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend that nisoldipine geomatrix (Sular geomatrix) be designated as non-formulary on the UF. This recommendation was based on the clinical effectiveness conclusion, and the determination that amlodipine (Norvasc, generics), felodipine (Plendil, generics) and generic nisoldipine coat core remain the most cost effective CCB agents on the UF compared to Sular Geomatrix.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of nisoldipine geomatrix and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for nisoldipine geomatrix (Sular geomatrix). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend: 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in TMOP and TRRx, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

5) DRUG CLASS REVIEW – OVERACTIVE BLADDER AGENTS (OABs)

Relative Clinical Effectiveness: The DoD P&T Committee evaluated the clinical effectiveness of the Overactive Bladder Agents (OABs); this class was first reviewed for UF placement in February 2006. There are nine marketed anticholinergic drugs for overactive bladder (OAB) in the US, darifenacin (Enablex), oxybutynin immediate release (IR) (Ditropan, generics), oxybutynin extended release (ER) (Ditropan XL; generics), oxybutynin transdermal (Oxytrol patch) solifenacin (Vesicare), tolterodine IR (Detrol), tolterodine ER (Detrol LA), trospium IR (Sanctura) and trospium ER (Sanctura XR).

Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the pharmaceutical agents included on the UF in that therapeutic class.

All nine drugs are FDA approved for the treatment of OAB with symptoms of urge incontinence, urgency and urinary frequency. Oxybutynin ER is also approved for the treatment of patients aged 6-years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g. spina bifida), but was not reviewed for this indication by the Committee. Only oxybutynin IR and ER are available in generic formulations.

Military Health System expenditures for the OAB class exceeded $74 million from July 07 to June 08. Tolterodine ER (Detrol LA) is the highest utilized OAB agent at the MTFs, followed by oxybutynin ER (Ditropan XL, generics). To review the full clinical effectiveness evaluation, see the OAB DoD Drug Class Review found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library. Note that rxnet is restricted to those with a ".mil" e-mail address.)

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusion:

a) Evaluation of clinically relevant differences in efficacy of the OAB agents at relieving urinary symptoms is hampered by the high placebo response rate (30-50%), varying use of non-pharmacologic measures such as bladder training and behavioral modification, and differing outcome measures used in clinical trials.

b) With regards to efficacy at reducing the number of urge incontinent episodes, urgency episodes, and micturation frequency, the available evidence does not support clinically relevant differences between oxybutynin IR (Ditropan, generics), oxybutynin ER (Ditropan XL, generics), oxybutynin patch (Oxytrol), tolterodine IR (Detrol), tolterodine ER (Detrol LA), trospium IR (Sanctura), trospium ER (Sanctura XR), solifenacin (Vesicare), and darifenacin (Enablex).

c) With regards to safety and tolerability, the following conclusions were made:

- There are no differences between the OAB drugs in terms of black box warnings (e.g., acute urinary or gastric retention, acute angle-closure glaucoma, and myasthenia gravis), listed in the product labeling.
- Oxybutynin IR had higher rates of withdrawals of therapy due to adverse events and occurrence of dry mouth then the other OAB agents, but no single agent has shown a clearly superior profile.
- The incidence of adverse events including dry mouth, and constipation, overall was lower with extended release preparations compared with immediate release formulations of the agents. The oxybutynin patch has been associated with pruritis and rash.
- The newer agents (trospium IR and ER, solifenacin, and darifenacin) do not appear to have a significantly lower incidence of dry mouth or constipation compared to extended-release forms of the older agents (oxybutynin ER, and tolterodine ER).
- All the OAB agents may cross the blood brain barrier and result in significant central nervous system effects, although this may be less likely with trospium IR and ER.
- Drug-drug interactions are less likely with trospium than the other agents.

d) With regards to tolerability and persistence rates, the following conclusions were made:

- Persistence rates for OAB medications reported in the medical literature are in general low (<10%); and a 2005 PEC analysis reported that only about 11% of MHS patients continued to obtain prescriptions for OAB medications on a regular basis after 1 year.
- An updated analysis performed by the Pharmacy Outcomes Research Team (PORT) included 35,121 DoD beneficiaries who were new users of OAB medications at any DoD pharmacy point of service from 1 Dec 06 to 31 May 07. Trospium ER was not commercially available at the time of the review and was not included in the analysis. The reported 1-year persistence rate with OAB therapy was 14% overall, with generally higher persistence for patients receiving newer agents and extended release versions of older agents, compared to those receiving immediate release versions of tolterodine and oxybutynin. About 28% of patients who were considered to be non-persistent continued to occasionally obtain prescription refills, consistent with use on an "as needed" rather than routine basis.

e) With regard to special populations, only oxybutynin IR and oxybutynin ER are approved for use in children ages 6 years and older. For pregnancy, oxybutynin IR, oxybutynin ER, and the oxybutynin patch are labeled as category B drugs, while the other OAB drugs are labeled as category C drugs.

Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in the OAB class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other

agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost Effectiveness Conclusion: The relative clinical effectiveness evaluation concluded that the newer OAB drugs darifenacin and solifenacin and the extended release formulations had higher persistence rates in the MHS than oxybutynin IR and tolterodine IR. Therefore, the cost effectiveness of the OAB agents was evaluated by CMA, cost effectiveness analysis (CEA), and by budget impact analysis (BIA). Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) the following:

a) Results from the CMA for the immediate release OAB agents (oxybutynin IR [Ditropan, generics], tolterodine IR [Detrol], and trospium IR [Sanctura]) revealed that oxybutynin IR was the most cost effective immediate release OAB agent overall.

b) Results from the CMA of extended release OAB agents (oxybutynin ER [Ditropan XL, generics], tolterodine ER [Detrol LA], trospium ER [Sanctura XR], oxybutynin transdermal [Oxytrol patch], darifenacin [Enablex], and solifenacin [Vesicare]) revealed that 1) trospium ER (Sanctura XR) was the most cost effective extended release OAB agent overall; and 2) when the price for generic formulations of oxybutynin ER (Ditropan XR) drops by 21.3% from the current price, oxybutynin ER will become the most cost-effective agent.

c) The results from a CEA comparing immediate release vs. extended release agents revealed that patients are more persistent with therapy when taking extended release products than when taking immediate release products. This is done at a significantly higher incremental cost per day of persistence gained by taking extended release products. However, the incremental cost per day of persistence gained is ~ 18% lower than when compared to MHS costs in 2005 when the OAB drugs were previously reviewed for UF placement.

d) The BIA evaluated the potential impact of scenarios with selected OAB agents designated formulary or non-formulary on the UF. Results from the BIA revealed that the scenario that designated tolterodine IR (Detrol) and trospium IR (Sanctura) as non-formulary under the UF was more favorable to the MHS.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 0 absent) to recommend to recommend that:

1) Oxybutynin IR (Ditropan, generics), oxybutynin ER (Ditropan XL, generics), oxybutynin patch (Oxytrol), tolterodine ER (Detrol LA), solifenacin (Vesicare), trospium ER (Sanctura XR), and darifenacin (Enablex) be classified as formulary on the UF.

2) Tolterodine IR (Detrol) and trospium IR (Sanctura) be designated as non-formulary under the UF, based on cost effectiveness.

All OAB drugs recommended for inclusion on the UF were covered by Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tolterodine IR (Detrol) and trospium IR (Sanctura) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for tolterodine IR (Detrol) and trospium IR (Sanctura). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD –The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. 2) That TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the OAB agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 0 absent) to recommend that 1) tolterodine ER (Detrol LA) continue to be designated as BCF; 2) that oxybutynin ER (Ditropan XL, generics) be designated as BCF; and that 3) oxybutynin IR (Ditropan, generics) be removed from the BCF, but maintained as formulary on the UF, starting the first Wednesday one week after the signing of the August 2008 DoD P&T Committee minutes by the Director, TMA. As a result of the above actions oxybutynin IR (Ditropan, generics) would no longer be designated as BCF, but maintained as formulary on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6) DRUG CLASS REVIEW – SELF-MONITORING BLOOD GLUCOSE TEST SYSTEMS (SMBGS) TEST STRIPS

Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the Self-Monitoring Blood Glucose Test Systems (SMBGS) test strips. The clinical evaluation included, but was not limited to, the requirements stated in the UF rule, 32 CFR 199.21(e)(1).The primary goal for the UF recommendation is to ensure uniform availability of quality SMBGS test strips across the MHS (MTF, TRRx, and TMOP points of service). SMBGS meters are not included as part of the TRICARE outpatient pharmacy benefit (they are included under the medical benefit) and are not the focus of the review; however provisions have been made to provide SMBGS meters at no cost to MHS beneficiaries.

The FDA classifies SMBGS test strips and meters as medical devices, rather than drugs, thus the focus of the clinical effectiveness review centered on differences in the technical aspects/attributes among the products. The P&T Committee had previously determined that all SMBGS test strips considered for inclusion on the UF must meet minimum technical standards relating to accuracy, blood sample size, availability of testing sites other than the fingertips, result time, memory capacity, ease of use (e.g., calibration and coding, large visual display), manufacturer customer support services, downloading capabilities, availability of data management software, and size.

The test strips included in the SMBGS class were those products approved by the FDA and available in the marketplace as of May 2008. Due to the complexity of evaluating the more than 40 commercially marketed SMBGS test strip brands, the number of test strips eligible of inclusion on the UF was determined by DoD P&T Committee minimum technical requirements, operational limitations of the existing TMOP and TRRx contract, and Federal Government contracting regulations.

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that:

a) With regard to efficacy, all meters that are approved by the FDA for licensing in the USA must meet the FDA standard of accuracy, which is a total analytical error of <5%. The International Organization for Standardization (ISO) also has standards. All the SMBGS test strips meeting the minimum technical requirements for inclusion on the UF met both FDA and ISO standards. There was insufficient published clinical trial data to determine if there were clinically relevant differences between the SMBGS test strips with regard to accuracy. The most common cause of inaccurate SMBGS test results is operator error.

b) With regard to calibration and coding, the SMBGS test strips with the lowest risk of coding/calibration errors (as they do not require coding) are the Ascensia Contour and Freestyle Lite test strips. The Accu-chek Aviva, Precision Xtra, and TrueTrack test strips require insertion of a coding chip or strip. The One Touch Ultra test strip requires manual coding.

c) With regard to blood sample size, the Freestyle Lite test strip requires 0.3 microliter (µL) blood; the Accu-check Aviva, Ascensia Contour, and Precision

Xtra require 0.6 µL; and the One Touch Ultra and TrueTrack test strips require 1 µL blood.

d) With regard to alternate site testing, the Accu-chek Aviva and Freestyle Lite strips are FDA-approved for testing at 5 alternate sites other than the fingertips, the Ascensia Contour strip is approved for 4 alternate sites, the Precision Xtra and One Touch Ultra strips are approved for 3 alternate sites, and the TrueTrack strip is approved for one alternate testing site other than the fingertips.

e) With regard to test result time, the Accu-chek Aviva, Ascensia Contour, Freestyle Lite, Precision Xtra, and One Touch Ultra provide test results within 5 seconds, while the TrueTrack strips provide test results in 10 seconds.

f) With regard to SMBGS test strip degradation due to heat and humidity, the Precision Xtra test strips are individually foil-wrapped; however patients with dexterity problems may have difficulty opening the foil wrappers.

g) With regard to safety, the Accu-chek Aviva and Freestyle Lite SMBGS test strips employ technology using glucose dehydrogenase (GDH) pyrroloquinolinequinone, which may cause falsely elevated blood glucose readings in patients receiving concomitant therapy with icodextrin-containing substances (Extrarenal peritoneal dialysis solution and the IV immunoglobulin product Octagam). SMBGS strips using GDH nicotinamide adenine dinucleotide [Precision Xtra], GDH flavin adenine dinucleotide [Ascensia Contour] or glucose oxidase technology [One Touch Ultra and TrueTrack] do not interfere with Extrarenal or Octagam.

h) With regard to special populations, those patients requiring intensive blood glucose monitoring (e.g., women with gestational diabetes, Type 1 diabetics, children and adults using insulin pumps) may prefer SMBGS test strips used in certain meters that can communicate wirelessly with insulin pumps.

i) With regard to provider opinion, a survey of MTF providers reported that accuracy and small blood sample size were the two technical requirements considered most important when comparing SMBGS.

j) With regard to therapeutic interchangeability, there is a high degree of therapeutic interchangeability between the SMBGS test strips meeting the DoD P&T Committee minimum technical requirements.

Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in the SMBGS test strip class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that for those SMBGS test strips meeting the minimum technical criteria, there were no clinically relevant differences between the agents. As a result, a CMA and BIA were conducted.

Relative Cost Effectiveness Conclusion: The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 0 absent) the following:

a) Results from the CMAs for the condition sets for both the 3 or less and 4 or more included on the UF revealed that Ascensia Contour was the most cost effective SMBG system while One Touch Ultra was the least cost effective. The ranking of most to least cost effective SMBGS test strips based on prices submitted for each condition set was: Ascensia Contour >TrueTrack > Freestyle Lite > Precision Xtra > Accu-chek Aviva > OneTouch Ultra.

b) The BIA evaluated the potential impact of scenarios with selected SMBGS products designated formulary or non-formulary on the UF. The BIA results showed that the scenario that designated the One Touch Ultra and TrueTrack self SMBGS as non-formulary on the UF was more favorable to the MHS.

*A. **COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the SMBGS test strips, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 2 opposed, 0 abstained, 1 absent) to recommend that:

1) Accu-chek Aviva, Precision Xtra, Freestyle Lite, and the Ascensia Contour SMBGS test strips be designated as formulary on the Uniform Formulary.

2) One Touch Ultra, TrueTrack, Accu-chek Comfort Curve, Accu-chek Compact Plus, Accu-chek Simplicity, Ascensia Autodisc, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle Test Strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check, and all store/private label brands not specified as formulary in "1" above be designated as non-formulary on the UF.

The SMBGS test strips are a medical device and subject to wholesale acquisition cost, rather than FCP pricing.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

*B. **COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for he SMBGS and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for the non-formulary SMBG systems listed in section A 2 above. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 120-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 120-day implementation period. 2) That TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the SMBGS. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 1 absent) to recommend that Precision Xtra be designated as the BCF SMBGS the first Wednesday one week after the signing of the August 2008 DoD P&T Committee minutes by the Director, TMA

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7) UTILIZATION MANAGEMENT – PRIOR AUTHORIZATIONS (PA)/ QUANTITY LIMITS (QL) / MEDICAL NECESSITY (MN)

Ondansetron (Zofran) – QL – Currently QLs are in place for the oral anti-emetics used for chemotherapy-induced and post-operative nausea and vomiting. Generic formulations of ondansetron tablets recently became available, with a corresponding reduction in cost. The current ondansetron QLs of 45 tabs per 90 days in the TMOP, and 15 tabs per 30 days in the TRRx are not sufficient to meet current FDA-approved dosage recommendations. The Committee recommended increasing the QLs for ondansetron 4 mg and 8 mg oral tablets and orally disintegrating tablets, to reflect the dosages recommended in the FDA-approved product labeling.

COMMITTEE ACTION: The P&T Committee voted (12 for, 2 opposed, 1 abstained, 0 absent) to approve ondansetron QLs of 60 tablets per 30 days at the retail point of service, and 180 tablets per 90 days at the mail order point of service.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8) RE-EVALUATION OF NON-FORMULARY AGENTS

The P&T Committee's process for re-evaluation of non-formulary agents established at the May 2007 meeting was approved by the Director, TMA on 24 June 2007. At the August 2008 meeting, the P&T Committee reviewed an updated list of non-formulary drugs identified that were: 1) from drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety and tolerability) compared to similar agents on the UF and not excluded from the UF based on clinical issues alone. The updated list is included in Appendix D.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 against, 1 abstained 0 absent) to recommend that the list of non-formulary agents in Appendix D be evaluated for UF status when pre-established criteria are met.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9) ITEMS FOR INFORMATION

TRICARE Management Activity (TMA), DoD PEC staff members, and PORT members briefed the P&T Committee on the following:

A. **Beneficiary Advisory Panel (BAP) Briefing** – CDR Ellzy briefed the members of the P&T Committee regarding the July 2008 BAP meeting. The P&T Committee was briefed on the BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation guidelines.

B. **Outcomes Research Reports** – *Fentanyl Patch Safety Program* – The PORT reported results of an analysis of the Fentanyl Patch Safety Program, which went into effect 1 Aug 2007. The program uses an automated prior authorization (PA) process to "look-back" at patients' pharmacy profiles; the dispensing process is stopped with a warning message if patients may not be opioid-tolerant based on prior dispensing of strong opioids. Pharmacists may override the warning using standard intervention and outcome codes after consulting with the prescriber or patient and/or taking into account information not available to the Pharmacy Data Transaction Service (PDTS) (i.e., prescriptions not paid for by DoD). Currently the program returns automated warning messages only at the retail network and mail order points of service.

   In general, the program appeared to reduce the use of fentanyl patch among seemingly opioid-naïve patients, without placing an undue burden on patients who may have been wrongly identified as opioid-naïve. Results of the analysis will be presented to the MHS Clinical Quality Forum.

C. **Implementation Status of UF Decisions** – The PEC briefed the members of the P&T Committee on the progress of implementation of drug classes reviewed for UF status since February 2005.

D. **Basic Core Formulary (BCF) / Extended Core Formulary (ECF) Review** – The PEC briefed the DoD P&T Committee on the efforts to implement electronic prescribing in the MHS. As part of the ongoing plan to systematically drugs represented on the BCF and ECF, the Committee periodically reviews recommendations for changes to the BCF and ECF, which will also assist with electronic prescribing. Further information will be presented at an upcoming meeting; no action necessary.

10)CLASS OVERVIEWS

Class overviews for the Nasal Allergy Drugs (comprised of the nasal antihistamines and nasal corticosteroids) and the inhaled Short Acting Beta Agonists were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness reviews and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the November 2008 meeting.

11)ADJOURNMENT

The second day of the meeting adjourned at 1200 hours on 13 Aug 2008. The next meeting will be 18-19 Nov 2008.

Appendix A – Attendance
Appendix B – Table of Medical Necessity Criteria
Appendix C – Implementation Status of UF Recommendations/Decisions
Appendix D – Non-Formulary Agents for Re-evaluation
Appendix E – Table of Abbreviations

SUBMITTED BY:

//signed//
Col John Kugler, MC
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

//signed// 24 Oct 08
S. Ward Casscells, III, M.D.

Appendix A – Attendance – (continued)

Others Present	
CAPT Miles Rudd	USPHS/IHS
Cathy Kelly, PharmD	Dept of Veteran's Affairs, Pharmacy Benefits Management
Lt Col James McCrary, MC, USAF	DoD PEC
LTC Chris Conrad, MC, USA	DoD PEC
CDR Matthew Carlberg, MC, USN	DoD PEC
MAJ Misty Carlson, MC, USA	DoD PEC
Maj Josh Devine, BSC, USAF	DoD PEC
LCDR Joe Lawrence, MSC, USN	DoD PEC
Lt Dean Kang, MSC, USN	DoD PEC Pharmacy Resident
HM2 Trishonya McMihelk	DoD PEC
Angela Allerman, Pharm.D.	DoD PEC
David Meade, Pharm.D.	DoD PEC
Harsha Mistry, Pharm.D.	DoD PEC
Eugene Moore, Pharm.D.	DoD PEC
Shana Trice, Pharm.D.	DoD PEC
Jeremy Briggs, Pharm.D.	DoD PEC – Pharmacy Operations Center

Appendix B – Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Desvenlafaxine (Pristiq) (Antidepressant-1s)	• The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
Nisoldipine geomatrix (Sular geomatrix) (Dihydropyridine Calcium Channel Blockers)	• The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
Tolterodine IR (Detrol), Trospium (Sanctura) (Overactive Bladder Drugs)	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
One Touch Ultra TrueTrack Accu-chek Comfort Curve Accu-chek Compact Plus Accu-chek Simplicity Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite Assure, Assure 3, Assure II, Assure Pro Bd Test Strips Chemstrip Bg Control AST Dextrostix Reagent Easygluco, Easypro Fast Take Freestyle test strips (other than Freestyle Lite) Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix Optium Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact Prestige Smart System Prodigy Quicktek Sidekick Sof-Tact Surestep Surestep Pro Test Strip Relion Ultima Uni-Check Plus all other store/private label brand strips not included on Uniform Formulary (see BCF/ECF column in Appendix C) **(Self-Monitoring Blood Glucose System (SMBGS) test strips)**	• Use of formulary alternatives is contraindicated • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

Appendix C – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 08	Self-Monitoring Blood Glucose Systems (SMBGS) test strips	▪ One Touch Ultra 2 strips (for One Touch Ultra 2, Ultra Mini, and Ultra Smart meters) ▪ TrueTrack strips (for TrueTrack meter) ▪ Accu-chek Comfort Curve strips (for Accu-chek Advantage meter) ▪ Accu-chek Compact Plus drum (for Accu-check Compact Plus meter) ▪ Accu-chek Simplicity, Ascensia Autodisk, Ascensia Breeze 2, Ascensia Elite, Assure, Assure 3, Assure II, Assure Pro, Bd Test Strips, Chemstrip Bg, Control AST, Dextrostix Reagent, Easygluco, Easypro, Fast Take, Freestyle test strips (other than Freestyle Lite), Glucofilm, Glucolab, Glucometer Dex, Glucometer Elite, Glucose Test Strip, Glucostix, Optium, Precision Pcx, Precision Pcx Plus, Precision Q-I-D, Precision Sof-Tact, Prestige Smart System, Prodigy, Quicktek, Sidekick, Sof-Tact, Surestep, Surestep Pro, Test Strip, Relion Ultima, Uni-Check ▪ Plus all other store/private label brand strips not included on Uniform Formulary (see the BCF/ECF column)	BCF	▪ Precision Xtra strips (for Precision Xtra meter) **Uniform Formulary SMBGS test strips** ▪ Accu-chek Aviva (for Accu-chek Aviva meter) ▪ Ascensia Contour (for Ascensia Contour meter) ▪ Freestyle Lite (for Freestyle Freedom Lite and Freestyle Lite meters)	pending approval	pending approval
Aug 08 (re-review; Feb 06 original review)	Overactive Bladder (OAB) Agents	▪ tolterodine IR (Detrol) ▪ trospium IR (Sanctura)	BCF	▪ tolterodine ER (Detrol LA) ▪ oxybutynin ER (Ditropan XL, generics) (Note: oxybutynin IR [generic Ditropan] removed from BCF, but still UF)	pending approval	pending approval
Aug 08 (update; reviewed Nov 05)	Antidepressants I	**Recommended for non-formulary status Aug 08** ▪ Desvenlafaxine (Pristiq)		No changes to BCF recommended Aug 08	pending approval	pending approval
		To remain NF: ▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	Currently BCF ▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jul 06	19 Jul 06 (180 days)

Aug 08 (update; reviewed Aug 05; also updated Nov 07)	Calcium Channel Blockers	**Recommended for non-formulary status Aug 08** ▪ nisoldipine geomatrix (Sular geomatrix)		No changes to BCF recommended Aug 08	pending approval	pending approval
		Previously non-formulary, recommended for UF status Nov 07 ▪ amlodipine besylate (Norvasc generic)		Recommended for addition to BCF Nov 07 ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	Currently BCF ▪ amlodipine besylate (Norvasc, generics) (Recommended at Nov 07 meeting) ▪ nifedipine ER (Adalat CC, generics) ▪ verapamil SR ▪ diltiazem ER (Tiazac, generics)	13 Oct 05	15 Mar 06 (150 days)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) (Note: raloxifene (Evista) removed from BCF, but still UF)	27 Aug 08	26 Nov 08 (90 days)
Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	27 Aug 08	26 Nov 08 (90 days)
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II	No changes to NF recommended Jun 08	BCF	**Recommended for addition to BCF Jun 08** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide) (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	27 Aug 08	29 Oct 08 (60 days)
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)		Currently BCF ▪ gemfibrozil	24 July 07	21 Nov 07 (120 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF	No change to BCF recommended Jun 08	27 Aug 08	29 Oct 08 (60 days)
		(No ABAs selected for NF placement at Nov 07 meeting)		Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-

Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF	No change to BCF recommended Jun 08	27 Aug 08	29 Oct 08 (60 days)
		To remain NF ▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)		▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** ▪ Zileuton ER (Zyflo CR)	BCF	No changes to BCF rec Jun 08	27 Aug 08	29 Oct 08 (60 days)l
		To remain NF ▪ zileuton (Zyflo)		Currently BCF ▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** ▪ olmesartan/amlodipine (Azor)	BCF	No change to BCF recommended Jun 08	27 Aug 08	29 Oct 08 (60 days)
		To remain NF ▪ valsartan amlodipine (Exforge)		No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel, generics) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)
Nov 07 (update,	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)

original review Nov 06)		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	No change to BCF recommended Nov 07	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
Aug 07 (new drug update, original review Nov 05)	Nasal Corticosteroids	**Recommended for non-formulary status Aug 07** ▪ fluticasone furoate (Veramyst)	BCF	▪ No change to BCF recommended Aug 07	17 Oct 07	19 Apr 06 (90 days)
		▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)		▪ fluticasone propionate (Flonase)	19 Jan 06	19 Dec 07 (60 days)
May 07 **re-review** (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)

May 07 **re-review** (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Monoamine Oxidase Inhibitors	▪ selegiline transdermal patch (Emsam)	ECF	▪ phenelzine (Nardil)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (update; reviewed Nov 06)	Dermatologic Topical Antifungals*	**Recommended for non-formulary status Nov 06:** 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)	BCF	No change to BCF recommended Nov 06	14 Jul 05	17 Aug 05 (30 days)

		▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)		▪ nystatin ▪ clotrimazole	17 Jan 07	18 Mar 07 (60 days)
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06 (re-classified Aug 07; and updated Jun 08; see above)	Misc Antihypertensive Agents (ACE/CCB combos now part of RAAs class)	(ACE/CCB combos now part of RAAs class) ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	(ACE/CCB combos now part of RAAs class) ▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
May 05	PDE5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

AD-1s: Antidepressant-1 Drugs; ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; LIP-1 = Antihyperlipidemic-1 Drugs; LIP-2 = Antihyperlipidemic-2 Drugs; MOAIs = Monoamine Oxidase Inhibitor Drugs; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; RAAs = Renin Angiotensin Antihypertensives Drugs; SMBGS: Self-Monitoring Blood Glucose Systems; TIBs = Targeted Immunomodulatory Biologics; TZDs= Thiazolidinediones

*The Dermatologic Topical Antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix D – Non-Formulary Drugs for Re-Evaluation

Generic Name	Brand Name	UF Class	Generic Y/N
Ciclopirox	Loprox	Antifungal – Derm	Y
Econazole	Spectazole	Antifungal – Derm	Y
Oxiconazole	Oxistat, Oxizole	Antifungal – Derm	N
Sertaconazole	Ertaczo	Antifungal – Derm	N
Sulconazole	Exelderm	Antifungal – Derm	N
Moexipril + HCTZ	Univasc, Uniretic	RAAs – ACEs	Y
Perindopril	Aceon	RAAs – ACEs	N
Ramipril	Altace	RAAs – ACEs	Y
Diltiazem ER	Cardizem LA	CCBs	N
Isradipine / CR	DynaCirc, DynaCirc CR	CCBs	N
Nicardipine / SR	Cardene, Cardene SR	CCBs	Y
Verapamil ER/HS	Verelan, Verelan PM, Covera HS	CCBs	Y
Tamsulosin	Flomax	Alpha Blocker – BPH	N
Azithromycin	Zmax	Macrolide/Ketolide Abx	N
Telithromycin	Ketek	Macrolide/Ketolide Abx	N
Beclomethasone	Beconase AQ	Nasal corticosteroids	N
Budesonide	Rhinocort aqua	Nasal corticosteroids	N
Triamcinolone	Nasacort AQ	Nasal corticosteroids	N
Bupropion	Wellbutrin XL	Antidepressant – 1s	Y
Duloxetine	Cymbalta	Antidepressant – 1s	N
Escitalopram	Lexapro	Antidepressant – 1s	N
Fluoxetine	Prozac weekly	Antidepressant – 1s	N
Fluoxetine	Sarafem	Antidepressant – 1s	Y
Paroxetine CR	Paxil CR	Antidepressant – 1s	Y
Felodipine/ enalapril	Lexxel	RAAs – ACE/CCB combos	N
Verapamil/ trandolapril	Tarka	RAAs – ACE/CCB combos	N
Pregabalin	Lyrica	GABA Analogs	N
EE 30 mcg; 0.15mg levonorgestrel	Seasonale	Contraceptives (M30)	Y
EE 35 mcg; 0.4mg norethindrone	Ovcon 35	Contraceptives (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon 50	Contraceptives (M50)	N
EE 20/30/35 mcg; 1mg norethindrone	Estrostep Fe	Contraceptives (Triphasic)	Y
EE 30/10mcg; 0.15mg levonorgestrel	Seasonique	Contraceptives (Extended cycle)	N
EE 20mcg; 1mg norethindrone	Loestrin 24 Fe	Contraceptives (M20)	N
Dolasetron	Anzemet	Anti-emetics	N

Abx = antibiotics; CCB = Calcium Channel Blockers; EE = ethinyl estradiol; HCTZ = hydrochlorothiazide; M = monophasic; RAAs = Renin Angiotensin Antihypertensives

Appendix E – Table of Abbreviations

AD-1	Antidepressant-1 drug class
AE	adverse event
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CC	coat core
CCB	calcium channel blocker
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CMA	cost minimization analysis
DHP	dihydropyridine
DoD	Department of Defense
DHP CCB	Dihydropyridine Calcium Channel Blocker drug class
ER	extended release
ESI	Express Scripts, Inc
FDA	Food and Drug Administration
FCP	Federal Ceiling Price
FY	fiscal year
GDH	glucose dehydrogenase
HA	Health Affairs
IR	immediate release
ISO	International Organization for Standardization
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
OAB	Over Active Bladder drug class
P&T	Pharmacy and Therapeutics
PA	prior authorization
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
QD	once daily
QL	quantity limit
SMBGS	Self-Monitored Blood Glucose System drug class
SNRI	Serotonin Norepinephrine Re-Uptake Inhibitor
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy Network
µL	microliter

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
June 2008

1) CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 1300 hours on 12 Jun 2008, and at 0800 hours on 13 Jun 2008 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2) ATTENDANCE

The attendance roster is found in Appendix A.

3) REVIEW MINUTES OF LAST MEETING

A. **Corrections to the minutes** – February 2008 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. **Approval of February minutes** – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the February 2008 DoD P&T Committee meeting on 30 Apr 2008.

4) REVIEW OF RECENTLY APPROVED AGENTS

A. Antilipidemic-II (LIP-2) – Fenofibrate meltdose (Fenoglide)

Relative Clinical Effectiveness – Fenofibrate meltdose (Fenoglide) is a new formulation of fenofibrate that is FDA-approved for treating hyperlipidemia and mixed dyslipidemia. To review the full clinical effectiveness evaluation, see the Fenoglide New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library; note that rxnet is restricted to those with a ".mil" e-mail address).

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that 1) there is no evidence to suggest that there are clinically relevant differences in the efficacy, safety and clinical outcomes of fenofibrate meltdose compared to other fenofibrate formulations, as they all contain the same active ingredient. 2) In terms of packaging and storage requirements, fenofibrate meltdose has advantages over fenofibrate insoluble drug delivery microparticle (IDD-P; Triglide) in that it is available in 90 count bottles and does not require dispensing in moisture-proof containers.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of fenofibrate meltdose in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of fenofibrate meltdose (Fenoglide). The cost effectiveness of Fenoglide was evaluated relative to the following agents: Triglide (currently the most cost effective UF fenofibrate) and Tricor. The results of the CMA showed that the projected

weighted average daily cost of Fenoglide was significantly lower than the weighted average daily cost of Triglide or Tricor.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that fenofibrate meltdose is cost effective relative to the evaluated agents in the LIP-2 class. The weighted average cost of Fenoglide is more cost effective relative to Triglide or Tricor.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (13 for, 0 opposed, 1 abstained, 1 absent) that: 1) fenofibrate meltdose (Fenoglide) be classified as formulary on the UF; and 2) the normal brand cost-share of $9.00 for fenofibrate meltdose (Fenoglide) be lowered to the generic formulary cost share of $3.00 in the retail and mail order points of service.

   The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." The objective is to maximize use of fenofibrate meltdose in the retail network and mail order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name fenofibrate meltdose will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena.

Fenofibrate meltdose (Fenoglide) was covered by the UF VARR submission at or below the FCP.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: BCF RECOMMENDATION*** – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 1 absent) to recommend that 1) fenofibrate meltdose (Fenoglide) be added to the BCF; and 2) that gemfibrozil (Lopid, generics) be maintained on the BCF. As a result of the above actions, fenofibrate IDD-P (Triglide) would no longer be designated as BCF, but maintained as formulary on the UF.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 1 absent) to recommend: 1) for

immediate implementation of the addition of fenofibrate meltdose (Fenoglide) to the BCF and the $3.00 co-pay reduction upon signing of the June 2008 DoD P&T Committee minutes by the Director, TMA; 2) that the special $3.00 co-pay that applied to fenofibrate IDD-P (Triglide) be terminated the first Wednesday following a 90-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Network Pharmacy (TRRx) programs; and 3) that TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Adrenergic Blocking Agents (ABAs) – Nebivolol (Bystolic)

Relative Clinical Effectiveness–Nebivolol is an Adrenergic Blocking Agent that is FDA-approved for treatment of hypertension. To review the full clinical effectiveness evaluation, see the Nebivolol New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that nebivolol (Bystolic) does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ABA agents currently included on the UF.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of nebivolol in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly to the following ABA medications: atenolol (Tenormin, generics), carvedilol extended release (Coreg CR) and metoprolol succinate extended release (Toprol XL, generics). Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2). A CMA was employed to determine the cost effectiveness of nebivolol (Bystolic) relative to atenolol, Coreg CR and metoprolol succinate ER. Results of the CMA showed that the projected weighted average daily cost of nebivolol was significantly higher than its ABA comparators.

Relative Cost Effectiveness Conclusion – P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 0 absent) that the weighted average daily cost of nebivolol (Bystolic) was significantly higher than the weighted average daily cost of atenolol, carvedilol extended release (Coreg CR), or metoprolol succinate extended release (Toprol XL, generics)

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness of nebivolol, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend that nebivolol (Bystolic) be designated as non-formulary on the UF. This recommendation was based on the clinical

effectiveness conclusion, and the determination that atenolol, carvedilol extended release and metoprolol succinate extended release remain the most cost effective ABA agents on the UF compared to nebivolol.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of nebivolol and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for nebivolol (Bystolic). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 0 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. Newer Antihistamines (NAs)– Levocetirizine (Xyzal)

Relative Clinical Effectiveness – Levocetirizine is a Newer Antihistamine that is the R-enantiomer of cetirizine. It is FDA-approved in adults and in children as young as six years of age for the treatment of seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria. To review the full clinical effectiveness evaluation, see the Levocetirizine New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that levocetirizine (Xyzal) did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other NAs included on the UF.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of levocetirizine (Xyzal) in relation to efficacy, safety, tolerability, and clinical outcomes of other agents in the class. A CMA was employed to determine the cost effectiveness of levocetirizine relative to other NAs: loratadine (OTC Claritin, generics), cetirizine (OTC Zyrtec, generics), fexofenadine (Allegra,

generics), and desloratadine (Clarinex). The results of the CMA revealed that the weighted average cost per day of levocetirizine is significantly higher than loratadine, cetirizine, and fexofenadine, but is significantly lower than the non-formulary NA desloratadine (Clarinex).

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that levocetirizine (Xyzal) is not cost effective relative to the other UF NAs.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of levocetirizine (Xyzal) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) to recommend that levocetirizine be designated as non-formulary under the UF.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of levocetirizine and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 2 absent) MN criteria for levocetirizine (Xyzal). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and no later than a 60-day implementation period at MTFs; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by Director, TMA.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

D. Leukotriene Modifier (LM) – Zileuton extended release (Zyflo CR)

Relative Clinical Effectiveness– Zileuton extended release (Zyflo CR) is a new formulation of zileuton immediate release (Zyflo) that is dosed twice daily, rather than four times daily. It is FDA-approved for the treatment of asthma in adults and in children as young as 12 years of age. To review the full clinical effectiveness evaluation, see the Zileuton extended release New Drug in Previously Reviewed

Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that zileuton extended release (Zyflo CR) did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other LMs included on the UF.

Relative Cost Effectiveness – The Committee evaluated the relative cost effectiveness of zileuton extended release (Zyflo CR) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the LM class. A CMA was employed to evaluate the cost effectiveness of zileuton extended release relative to montelukast (Singulair), zafirlukast (Accolate), and zileuton immediate release (Zyflo). The results of the CMA demonstrated that the projected weighted average daily cost of zileuton extended release was significantly higher than the weighted average daily cost of the comparators within the LM class.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that zileuton extended release (Zyflo CR) is not cost effective relative to the other agents in the LM class. The weighted average cost of montelukast (Singulair), zafirlukast (Accolate) and zileuton immediate release (Zyflo) is more cost effective relative to zileuton extended release.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of zileuton extended release (Zyflo CR) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) to recommend that zileuton extended release be designated as non-formulary under the UF.

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of zileuton extended release and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 0 abstained, 2 absent) MN criteria for zileuton extended release (Zyflo CR). (See Appendix B for full MN criteria).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and no later than a 60-day implementation period at MTFs; and 2) TMA send a letter to beneficiaries affected by this UF decision. The

implementation period will begin immediately following approval by Director, TMA.

Director, TMA, Decision: ☒ Approved ☐ Disapproved
Approved, but modified as follows:

E. Antilipidemic – I (Lip-1) – Simvastatin/niacin extended release (Simcor)

Relative Clinical Effectiveness – Simcor is the combination of 40 mg simvastatin (Zocor, generics) with 500-, 750- or 1000- mg of niacin extended release (Niaspan). It is approved by the FDA for patients with hyperlipidemia to raise HDL concentrations, and to lower LDL, triglyceride, non-HDL, and total cholesterol concentrations, when monotherapy is inadequate. To review the full clinical effectiveness evaluation, see the Simcor New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that there is insufficient evidence to suggest if there are clinically relevant differences between simvastatin/niacin extended release (ER; Simcor) and the other statins and niacin in terms of efficacy, and that in terms of safety and tolerability, Simcor appears comparable to giving the simvastatin and niacin components separately.

Relative Cost Effectiveness - The P&T Committee evaluated the relative cost effectiveness of simvastatin/niacin ER (Simcor) in relation to efficacy, safety, tolerability, and clinical outcomes of other agents in the LIP-1 class. A CMA was employed to evaluate the cost effectiveness of simvastatin/niacin ER relative to simvastatin (Zocor, generics), niacin ER (Niaspan), lovastatin/niacin ER (Advicor) and the combination of the individual components of Simcor (simvastatin plus Niaspan). The results of the CMA showed that the projected weighted average daily cost of Simcor was significantly less than the weighted average daily cost of its comparators.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that simvastatin/niacin ER (Simcor) is cost effective relative to the evaluated agents in the LIP-1 class.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of simvastatin/niacin ER (Simcor) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) to recommend that simvastatin/niacin ER be classified as formulary on the UF.

Simvastatin/niacin ER was covered by a UF VARR submission at or below the FCP

Director, TMA, Decision: ☑ Approved ☐ Disapproved
Approved, but modified as follows:

F. Glaucoma Agents – Brimonidine 0.02% / timolol maleate 0.05% (Combigan)

Relative Clinical Effectiveness – Combigan is a combination ophthalmic product that contains the alpha-2 adrenergic agonist brimonidine 0.02% (Alphagan, generics) with the beta blocker timolol maleate 0.05% (Timoptic, generics). Combigan is approved for twice daily use for the reduction of elevated intraocular pressure in patients with ocular hypertension or glaucoma who require adjunctive or replacement therapy. To review the full clinical effectiveness evaluation, see the Combigan New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that while brimonidine/timolol (Combigan) offers a convenience to the patient in terms of ease of administration, there is currently insufficient evidence to suggest if there are clinically relevant differences between Combigan and the other Glaucoma Agents in terms of efficacy. In terms of safety and tolerability, Combigan appears comparable to administering brimonidine and timolol as separate products dosed twice daily.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of brimonidine/timolol ophthalmic solution (Combigan) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. A CMA was employed to evaluate the cost effectiveness of Combigan relative to timolol maleate (Timoptic, generics), brimonidine (Alphagan, generics), dorzolamide/timolol (Cosopt), and the single ingredient agents of Combigan (timolol maleate and brimonidine). The results of the CMA showed that the projected weighted average daily cost of Combigan was significantly lower than its comparators.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that the projected weighted average daily cost of Combigan was significantly lower than the weighted average daily cost of dorzolamide/timolol (Cosopt), or the pairings of the individual brimonidine and timolol components.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of brimonidine/timolol maleate (Combigan) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) to recommend that brimonidine/timolol maleate be classified as formulary under the UF.

Brimonidine/timolol maleate was covered by the UF VARR submission at or below the FCP.

Director, TMA, Decision: ☑ Approved ☐ Disapproved
Approved, but modified as follows:

G. Renin Angiotensin Antihypertensives (RAAs) – Olmesartan / amlodipine (Azor)

Relative Clinical Effectiveness – Azor is the combination of the angiotensin receptor blocker (ARB) olmesartan with the dihydropyridine calcium channel blocker (DHP CCB) amlodipine. It is FDA-approved for treating hypertension. To review the full clinical effectiveness evaluation, see the Azor New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library). .

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that while olmesartan/amlodipine (Azor) offers a convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other renin angiotensin antihypertensives included on the UF.

Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of olmesartan/amlodipine (Azor) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the RAA class, particularly the ARBs. A CMA was employed to evaluate the cost effectiveness of olmesartan/amlodipine relative to telmisartan (Micardis), the BCF ARB; generic amlodipine (Norvasc), a BCF DHP-CCB; valsartan/amlodipine (Exforge); and to the combination of the individual components of telmisartan plus generic amlodipine. The results of the CMA demonstrated that the projected weighted average daily cost of Azor was significantly higher than the weighted average daily cost of combined individual agents (telmisartan plus generic amlodipine).

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that olmesartan/ amlodipine is not cost effective relative to the other UF agents in the RAA class. The weighted average cost of combined individual agents (the BCF ARB telmisartan and BCF generic DHP CCB amlodipine) is more cost effective relative to Azor.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of olmesartan/amlodipine (Azor) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) to recommend that olmesartan/amlodipine be designated as non-formulary under the UF.

   Director, TMA, Decision: ☑ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of olmesartan/amlodipine and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee

recommended (13 for, 0 opposed, 0 abstained, 2 absent) MN criteria for olmesartan/amlodipine (Azor). (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and no later than a 60-day implementation period at MTFs; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

H. Renin Angiotensin Antihypertensives (RAAs) – Aliskiren / hydrochlorothiazide (Tekturna HCT)

Background – Tekturna HCT contains the renin inhibitor aliskiren with the diuretic hydrochlorothiazide (HCTZ). It is FDA-approved for treating hypertension. Preliminary results of clinical outcomes trials with aliskiren evaluating benefits in addition to blood pressure reduction have been positive. To review the full clinical effectiveness evaluation, see the Tekturna HCT New Drug in Previously Reviewed Classes monograph found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that while aliskiren/HCTZ offers a convenience to the patient in terms of decreased tablet burden and simplified medication regimen, there is insufficient evidence to suggest that the blood pressure lowering effect of aliskiren/HCTZ would be significantly greater than that achieved with other antihypertensive fixed-dose combinations. In terms of safety and tolerability, Tekturna HCT appears comparable to administering the aliskiren and HCTZ components separately.

Relative Cost Effectiveness - The P&T Committee evaluated the relative cost effectiveness of aliskiren/HCTZ (Tekturna HCT) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the RAA class, particularly the ARBs. A CMA was employed to evaluate the cost effectiveness of aliskiren/HCTZ relative to the renin inhibitor aliskiren (Tekturna) and the ARBs, which were evaluated at the May and August 2007 DoD P&T Committee meetings. The results of the CMA showed that the projected weighted average daily cost of aliskiren/HCTZ was higher than the weighted average daily cost of the ARBs designated as formulary on the UF, but similar to the UF agent aliskiren (Tekturna).

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 0 opposed, 0 abstained, 2 absent) that the projected weighted average daily cost of aliskiren/HCTZ (Tekturna HCT) was comparable to the renin inhibitor aliskiren, and higher than the weighted average daily cost of ARBs designated as formulary within the RAA class on the UF.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of aliskiren/HCTZ (Tekturna HCT) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, 2 absent) that although aliskiren/HCTZ was somewhat more costly relative to the ARBs designated as formulary in the RAA class, Tekturna HCT was recommended to be classified as formulary on the UF, due to the novel mechanism of action of the aliskiren component and preliminary positive outcomes data.

Aliskiren/hydrochlorothiazide was covered by the UF VARR submission at or below the FCP.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

5) DRUG CLASS REVIEW – 5-HYDROXYTRYPTAMINE AGONISTS (TRIPTANS)

Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the eight marketed 5-hydroxytryptamine agonists (triptans) in the US, almotriptan (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), sumatriptan (Imitrex), sumatriptan/naproxen (Treximet), rizatriptan (Maxalt), and zolmitriptan (Zomig). None of the triptans are available in generic formulations, although generic formulations of sumatriptan are expected in early 2009.

MHS expenditures for the triptans were approximately $70 million for the time period of May 2007 to April 2008. In terms of total quantity dispensed between May 2007 and April 2008, sumatriptan is the highest utilized triptan in the MHS (~150,000 tablets dispensed/month), followed by zolmitriptan (~60,000 tablets/month), and rizatriptan (~45,000 tablets/month). To review the full clinical effectiveness evaluation, see the Triptan DoD Drug Class Review found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusion:

a) With regards to efficacy at providing pain relief at 2 hours,1) rizatriptan 10 mg (Maxalt) appears superior to the other triptans; 2) almotriptan (Axert), eletriptan (Relpax), sumatriptan (Imitrex) and zolmitriptan (Zomig) have comparable relative effectiveness; 3) frovatriptan (Frova) appears inferior to the other triptans, although these results are based on limited data; 4) naratriptan (Amerge) appears inferior to the other triptans; and 5) sumatriptan/naproxen (Treximet) appears superior to sumatriptan 85 mg, but there is insufficient evidence to suggest clinically relevant differences between Treximet and the other triptans.

b) With regards to other efficacy endpoints, 1) rizatriptan 10 mg (Maxalt) and almotriptan 12.5 mg (Axert) are superior to the other triptans for pain free response at 24 hours; and 2) rizatriptan 10 mg is superior to the other triptans for pain-free response at 2 hours.

c) With regards to safety and tolerability, almotriptan (Axert) and naratriptan (Amerge) had the most favorable adverse event profiles compared to the other triptans. There is only limited data for frovatriptan from the product labeling.

Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

Relative Cost Effectiveness Conclusion: The cost effectiveness of the triptan agents was evaluated by CMA, cost effectiveness analysis (CEA), and by budget impact analysis (BIA). Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) the following:

a) Results from the triptan CMA revealed that sumatriptan/naproxen (Treximet) was the most cost effective agent overall. However, sumatriptan (Imitrex) is expected to become the most cost-effective triptan when generic formulations reach the market in early 2009.

b) Results from the 2 hour pain response CEA revealed that 1) sumatriptan/naproxen (Treximet), eletriptan (Relpax) and rizatriptan (Maxalt) formed the efficiency frontier and are the most cost-effective agents; and 2) when the price for generic formulations of sumatriptan (Imitrex) drops below 70% of the current price, sumatriptan and rizatriptan will become the most cost-effective agents.

c) Results from the 2 hour pain-free response CEA yielded results similar to the 2 hour pain response.

d) The BIA evaluated the potential impact of scenarios with selected triptans designated formulary or non-formulary on the UF. Results from the BIA revealed that the scenario that designated almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge) as non-formulary under the UF was more favorable to the MHS.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the triptans, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, and 1 absent) to recommend that:

1) Sumatriptan (Imitrex), sumatriptan/naproxen (Treximet), eletriptan (Relpax), rizatriptan (Maxalt), and zolmitriptan (Zomig) be classified as formulary on the UF.

2) Almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge) be designated as non-formulary under the UF, based on cost effectiveness.

All triptan drugs recommended for inclusion on the UF were covered by Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP). (One of the triptan drugs recommended for non-formulary status was also covered by a UF-VARR at or below the FCP, but was not considered cost-effective.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for almotriptan (Axert), frovatriptan (Frova), and naratriptan (Amerge), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) MN criteria for almotriptan, frovatriptan, and naratriptan. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD –The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. 2) That TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the triptan agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (12 for, 1 opposed, 1 abstained, and 1 absent) to recommend that 1) rizatriptan (Maxalt) be designated as BCF immediately upon signing of the June 2008 DoD P&T Committee minutes by the Director, TMA; 2) sumatriptan (Imitrex oral tablets and one injectable sumatriptan formulation be designated as BCF when multi-source generic formulations that are cost effective reach the marketplace. As a result of the above actions, zolmitriptan (Zomig) would no longer be designated as BCF, but maintained as formulary on the UF.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: QUANTITY LIMIT (QL) RECOMMENDATIONS – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 1 absent) to 1) to recommend QLs for sumatriptan 85 mg/naproxen 500 mg (Treximet) of 9 tablets per 30 days and 27 tablets per 90 days; 2) to recommend QLs for sumatriptan (Imitrex) 4 mg injection of 9 syringes per 30 days and 24 syringes per 90 days; and 3) to maintain the existing QLs for the other triptans.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

6) 6) DRUG CLASS REVIEW – OSTEOPOROSIS AGENTS

Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the osteoporosis agents currently marketed in the US. The individual drugs included in the class are listed below:

- *Bisphosphonates*: alendronate (Fosamax), alendronate/vitamin D (Fosamax plus D), ibandronate (Boniva), risedronate (Actonel), and risedronate/calcium (Actonel with calcium). Intravenous (IV) zoledronic acid (Reclast) and IV ibandronate (Boniva) were not part of the UF review, as they are not included as a TRICARE pharmacy benefit.

  Selective estrogen receptor modulators (SERMs): raloxifene (Evista)

- *Parathyroid hormone(PTH) 1-34 amino acids:* teriparatide (Forteo)

- *Calcitonin nasal sprays:* calcitonin-salmon (Miacalcin) and recombinant calcitonin (Fortical)

Generic formulations of alendronate 2800 IU (Fosamax) became commercially available in 2008. There are no generic formulations of any of the other osteoporosis agents. All the agents are approved for treating osteoporosis; raloxifene (Evista) is also approved for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis or those at high risk of invasive breast cancer.

MHS expenditures from May 2007 to April 2008 exceeded $200 million, of which over $151 million was attributed to the bisphosphonates alone. In terms of 30-day equivalent prescriptions dispensed, alendronate is the highest utilized osteoporosis agent (approximately 120,000/month), followed by risedronate (approximately 40,000/month) and raloxifene (less than 40,000/month). To review the full clinical effectiveness evaluation, see the Osteoporosis DoD Drug Class Review found at https://rxnet.army.mil/ (Forum: File Library; Folder: DoD P&T library).

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that:

a) With regard to changes in bone mineral density (BMD), all the drugs in the bisphosphonates, SERMs, PTH derivative, and calcitonin subclasses increase

BMD, but superiority of one drug over another cannot be determined by BMD changes alone.

b) With regard to fracture risk reduction, 1) the supporting evidence for the bisphosphonates is stronger than that available for raloxifene (Evista), teriparatide (Forteo) and the calcitonin nasal sprays (Fortical and Miacalcin); and 2) there is insufficient evidence to determine if there are clinically relevant differences between the drugs in each osteoporosis subclass.

c) With regard to the orally administered bisphosphonates, 1) the bisphosphonates reduce the risk of vertebral fractures to a similar degree, but the data is limited to daily dosing and there is insufficient evidence to determine if there are clinically relevant differences in fracture risk reduction with extended interval dosing regimens; 2) risedronate (Actonel) and IV zoledronic acid have evidence from adequately powered clinical trials that they reduce the risk of non-vertebral and hip fractures compared to the other bisphosphonates; and 3) there is insufficient evidence to suggest clinically relevant differences between the orally administered bisphosphonates in preventing fractures.

d) With regard to the SERM raloxifene (Evista) and the calcitonin nasal sprays, 1) both subclasses reduce the risk of vertebral fractures, but the data is more limited than that available with the bisphosphonates; and 2) there is no data to suggest clinically relevant efficacy differences between calcitonin-salmon (Miacalcin) and recombinant calcitonin (Fortical).

e) With regard to the PTH derivative teriparatide (Forteo), 1) there is evidence from one clinical trial supporting vertebral and non-vertebral fracture risk reduction; and 2) teriparatide is potentially beneficial in reducing fracture risk in patients experiencing fractures despite bisphosphonate therapy.

f) With regard to safety of the oral bisphosphonates, 1) there is no evidence to suggest that there are clinically relevant differences between alendronate (Fosamax), risedronate (Actonel) and ibandronate (Boniva) in the incidence of gastrointestinal complaints; 2) the overall incidence of osteonecrosis of the jaw with the oral agents is low; and 3) long-term safety data extending out to 10 years is available with alendronate (Fosamax).

g) With regard to tolerability of the oral bisphosphonates, a retrospective observational cohort analysis of 23,044 DoD beneficiaries performed by the Pharmacy Operations Outcomes Team (PORT) compared medication persistence between weekly vs. monthly dosing regimens, based on prescription claims during the year following the initial prescription. The study included all DoD beneficiaries filling initial prescriptions for bisphosphonates at the retail and mail order points of service from 1 Aug 06 to 31 Jan 07. Results of the multivariate logistic regression model were adjusted for age, gender, point of service, TRICARE region, and number of concomitant maintenance medications. The odds of a patient being persistent with treatment (≥80% of days covered based on cumulative days supply) were 18% higher among monthly users compared to weekly users of bisphosphonates (OR 1.18; 95% CI 1.12-1.25). Improved persistence on bisphosphonate therapy has been shown to be associated with a

reduced risk of fracture based on observational data, although data from randomized controlled trials supporting a causal relationship are not yet available.

h) With regard to safety and tolerability of the other osteoporosis subclasses, each subclass (SERM, calcitonin and PTH derivative) has unique adverse event profiles.

i) With regard to other factors of the calcitonin nasal sprays, there are no clinically relevant differences between calcitonin-salmon (Miacalcin) and recombinant calcitonin (Fortical), with the exception of differences in the preservative and ease of administration.

Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that: 1) the bisphosphonates are highly clinically interchangeable with each other for the treatment of osteoporosis; 2) there is evidence that the extended dosing interval (monthly) bisphosphonates may yield greater rates of persistence than the weekly formulations; 3) the two calcitonin products are formulated with identical molecules and are highly clinically interchangeable for their osteoporosis indications; and 4) teriparatide and raloxifene occupy treatment niches for selected patients. As a result, CMAs were conducted for the bisphosphonate and calcitonin subclasses to compare the relative cost effectiveness of these agents. Additionally a CEA was performed to evaluate the extended dosing interval bisphosphonates. The SERM and parathyroid agents were compared to the other subclasses in a further cost analysis.

Relative Cost Effectiveness Conclusion: The P&T Committee concluded (14 for, 1 opposed, 0 abstained, 0 absent) the following:

a) Results from the bisphosphonate CMA revealed that ibandronate (Boniva) was the most cost effective agent overall. However, generic formulations of alendronate (Fosamax) have recently become available, and alendronate is expected to become the most cost effective oral bisphosphonate when the generic exclusivity period ends in the third quarter, 2008.

b) Results from the nasal calcitonin CMA revealed that recombinant calcitonin (Fortical) is significantly more cost effective than salmon-calcitonin (Miacalcin).

c) Results from the extended dosing interval bisphosphonate CEA revealed: 1) based on available published literature, improved persistence with extended cycle bisphosphonates would likely result in a small decrease in the risk of fractures; 2) the incremental annual cost per patient using extended dosing interval bisphosphonates is modest; and 3) while extended dosing interval products are slightly more costly, these agents remain cost effective for the treatment of osteoporosis.

d) The cost comparison of teriparatide (Forteo) and raloxifene (Evista) to the other osteoporosis subclasses concluded that 1) raloxifene is slightly more costly than

the bisphosphonates and calcitonin; and 2) teriparatide is significantly more costly than bisphosphonates and calcitonin.

e) The BIA evaluated the potential impact of scenarios with selected bisphosphonates, teriparatide (Forteo), and calcitonin products designated formulary or non-formulary on the UF. The BIA results showed that the scenario that designated the salmon-calcitonin (Miacalcin) as non-formulary on the UF was more favorable to the MHS.

*A. **COMMITTEE ACTION: UF RECOMMENDATION*** – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the osteoporosis agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 1 opposed, 2 abstained, and 0 absent) to recommend that: 1) alendronate (Fosamax), alendronate/vitamin D (Fosamax plus D), risedronate (Actonel), risedronate with calcium (Actonel with calcium), ibandronate (Boniva), raloxifene (Evista), teriparatide (Forteo), and recombinant calcitonin (Fortical) be maintained as formulary on the UF and that 2) salmon-calcitonin (Miacalcin) be designated as non-formulary on the UF. The Committee member casting the dissenting vote felt that an additional agent, teriparatide, should also be classified as NF, due to existing low MHS utilization (less than 5,000 patients); that its clinical niche would allow for unique MN criteria specific to this agent; and that NF placement would allow for additional cost avoidance.

Despite the higher cost of raloxifene (Evista) and teriparatide (Forteo) compared to the other osteoporosis agents, the Committee recommended designating these agents as formulary on the UF, due their clinical niche (reduction in risk of invasive breast cancer; and non-oral administration route and approval for severe osteoporosis, respectively), and the expectation that several SERMs and PTH hormone derivatives currently under investigation will reach the marketplace in 2009-2010.

All osteoporosis drugs recommended for inclusion on the UF were covered by Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP), with the exception of raloxifene, teriparatide, and recombinant calcitonin. These three osteoporosis agents were recommended for inclusion on the UF without UF VARR quotes, due to their unique indications and place in therapy.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

*B. **COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for salmon-calcitonin (Miacalcin) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) MN criteria for Miacalcin. (See Appendix B for full MN criteria).

Director, TMA, Decision: ☒ Approved ☐ Disapproved
Approved, but modified as follows:

*C. **COMMITTEE ACTION: IMPLEMENTATION PERIOD*** –The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. 2) That TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

Director, TMA, Decision: ☒ Approved ☐ Disapproved
Approved, but modified as follows:

*D. **COMMITTEE ACTION: BCF RECOMMENDATION*** – The P&T Committee considered the BCF status of the osteoporosis agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (9 for, 4 opposed, 2 abstained, and 0 absent) to recommend that alendronate (Fosamax) and ibandronate (Boniva) be designated as BCF. As a result of the above actions, raloxifene (Evista) would no longer be designated as BCF, but maintained as formulary on the UF.

Director, TMA, Decision: ☒ Approved ☐ Disapproved
Approved, but modified as follows:

7) UTILIZATION MANAGEMENT - PRIOR AUTHORIZATIONS (PA)/ QL / MEDICAL NECESSITY (MN)

A. Targeted Immunomodulatory Biologics (TIBs)

Adalimumab (Humira) Juvenile Idiopathic Arthritis (JIA) new indication - Administrative Action – Adalimumab received an additional indication from the FDA for children aged 4 to 17 years to reduce the signs and symptoms of moderate to severely active polyarticular JIA. Adalimumab may be used with or without methotrexate for this indication. The FDA-approved JIA indication will be added to the PA for Humira.

B. Phosphodiesterase type 5 inhibitors (PDE5s)

Tadalafil (Cialis) QL – Administrative Action – Tadalafil was recently approved in 2.5 mg and 5 mg dosages for daily use for erectile dysfunction (ED). Health Affairs Policy 98-04 was rescinded in Nov 2003 to state that prior authorization was no longer required for PDE-5 inhibitors in the treatment of ED for males older than 50 years of age. The HA policy still maintains QLs collectively for all strengths of sildenafil, tadalafil and vardenafil of no more than 18 tablets of any combination of these medications per 90-day supply in the TMOP, and no more than 6 tablets of any

combination of these medications per 30-day supply in the Retail Network. The existing QLs for tadalafil will apply to the new 2.5 mg and 5 mg dosages.

C. **LIP-2s – Colesevelam (Welchol) MN Criteria** – The Committee discussed the MN criteria for colesevelam with regard to a new FDA-approved indication for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The LIP-2 drug class was previously reviewed for UF placement in May 2007; at the time of the meeting, colesevelam was solely approved for lowering elevated LDL concentrations in primary hyperlipidemia. The clinical trial used to gain FDA-approval of colesevelam for T2DM evaluated the drug as adjunctive therapy to other glucose-lowering drugs, and did not evaluate colesevelam use as monotherapy. The Committee agreed that there were other treatments for T2DM with greater efficacy than colesevelam.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 1 absent) to maintain the current MN criteria for colesevelam.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. **Aprepitant (Emend) – QL** – Aprepitant was approved by the FDA in a new 40 mg strength solely indicated for prevention of post-operative nausea and vomiting. Currently, QLs apply to the aprepitant formulation approved for prevention of chemotherapy-induced nausea and vomiting; QLs also apply to other antiemetics.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 1 absent) to approve the QLs for aprepitant 40 mg of 1 capsule/prescription fill at the retail and mail order points of service.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8) ITEMS FOR INFORMATION

A. Outcomes Research Reports

1) *Step Therapy* – To support the P&T Committee's consideration of a potential step therapy requirement in the triptan drug class, the PORT reported results of an analysis of changes in medication usage attributable to step therapy/prior authorization requirements for newer sedative hypnotics (effective date 1 Aug 07) and proton pump inhibitors (effective date 24 Oct 07). The step therapy / prior authorization program, which requires new users of non-preferred medications to try a preferred agent before receiving a non-preferred agent, appears highly effective at promoting use of preferred agents. However, the Committee agreed that more information is needed concerning the effect of the program on beneficiaries. A study of outcomes associated with step therapy interventions is

under development and is currently being considered by the MHS Scientific Advisory Panel.

2) *Fentanyl Patch Safety Program* – The PORT notified the P&T Committee of implementation issues detected during data collection for a study of the Fentanyl Patch Safety Program. These issues were corrected, bringing the program into line with requirements previously set by the P&T Committee. Preliminary results of the analysis are scheduled for the next P&T meeting.

9) ADJOURNMENT

The second day of the meeting adjourned at 1400 hours on 13 Jun 2008. The next meeting will be 12-13 Aug 2008.

Appendix A – Attendance
Appendix B – Table of Medical Necessity Criteria
Appendix C – Implementation Status of UF Recommendations/Decisions
Appendix D – Table of Abbreviations

SUBMITTED BY:

//signed//
Col John Kugler, MC
DoD P&T Committee Chair
25 Aug 08

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

//signed//
S. Ward Casscells, III, M.D.
27 Aug 08

Appendix A – Attendance

Voting Members Present	
Col John Kugler, MC, USA	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
Major Jeremy King, MC	Air Force, OB/GYN Physician
Major William Hannah, MC	Air Force, Internal Medicine Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CAPT Stephanie Simon, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
Col Karl R. Kerchief, MC *for* Major Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC (P) Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Lt Col Thom Bacon *for* CAPT William Blanche, MSC, USN	DoD Pharmacy Operations Directorate, TMA
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs
Voting Members Absent	
CDR David Tanen, MC	Navy, Physician at Large
LCDR Michelle Perelló, MC	Navy, Internal Medicine Physician
Non-Voting Members Present	
COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Ms. Carol Cooper	Deputy General Counsel, TMA
LCDR Thomas Jenkins, MSC, USN	TMA Aurora
Non-Voting Members Absent	
Martha Taft	Health Plan Operations, TMA

Appendix A – Attendance – (continued)

Others Present	
CDR James Ellzy, MC, USN	Vice DoD P&T Committee Chair
CDR Matthew Carlberg, MC, USN	DoD PEC
Lt Col James McCrary, MC, USAF	DoD PEC
LTC Chris Conrad, MC, USA	DoD PEC
Maj Josh Devine, BSC, USAF	DoD PEC
CPT Josh Napier, MC, USA	DoD PEC
Angela Allerman, Pharm.D.	DoD PEC
David Meade, Pharm.D.	DoD PEC
Harsha Mistry, Pharm.D.	DoD PEC
Eugene Moore, Pharm.D.	DoD PEC
Shana Trice, Pharm.D.	DoD PEC
Dean Valibhai, Pharm.D.	DoD PEC – Pharmacy Operations Center
Jeremy Briggs, Pharm.D.	DoD PEC – Pharmacy Operations Center
Major Mike Lee, BSC	Air Force, Alternate Pharmacist Officer
LCDR Timothy Thompson	Navy, Pharmacy Officer Alternate
CAPT Travis Watts	USPHS/HIS
Lisa McNair	DoD Pharmacy Operations Directorate – TMA

Appendix B – Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
Levocetirizine (Xyzal) **Newer Antihistamines**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure.
Nebivolol (Bystolic) **Adrenergic Blocking Agent**	• Use of formulary alternatives is contraindicated • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
Olmesartan / amlodipine (Azor)	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives.
Calcitonin-salmon nasal spray (Miacalcin) **Osteoporosis Agents**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
Almotriptan (Axert), Frovatriptan (Frova), Naratriptan (Amerge) **Triptans**	• Use of formulary alternatives is contraindicated • The patient has experienced or is likely to experience significant adverse effects from formulary alternatives. • Formulary agents have resulted or are likely to result in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
Zileuton extended release (Zyflo CR) **Leukotriene Modifiers**	• Use of formulary alternatives is contraindicated • The patient has experienced significant adverse effects from formulary alternatives. • Formulary agents have resulted in therapeutic failure. • The patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

Appendix C – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Jun 08	Osteoporosis Agents	▪ calcitonin salmon nasal spray (Miacalcin)	BCF	▪ alendronate (Fosamax) ▪ ibandronate (Boniva) ▪ (Note: raloxifene (Evista) removed from BCF, but still UF)	Pending approval	Pending approval
Jun 08	Triptans	▪ almotriptan (Axert) ▪ frovatriptan (Frova) ▪ naratriptan (Amerge)	BCF	▪ rizatriptan (Maxalt), immediate upon signing of the minutes ▪ sumatriptan oral and one injectable formulation, when multi-source generics are available	Pending approval	Pending approval
Jun 08 (update; reviewed May 07)	Antilipidemic Agents II		BCF	**Recommended for addition to BCF Nov 07** ▪ fenofibrate meltdose (Fenoglide), to replace fenofibrate IDD-P (Triglide)	Pending approval	Pending approval
		To remain NF ▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)		Currently BCF ▪ gemfibrozil ▪ (Note: fenofibrate IDD-P (Triglide) removed from BCF but still UF)	24 July 07	21 Nov 07 (120 days)
Jun 08 (update; reviewed Nov 07)	Adrenergic Blocking Agents	**Recommended for non-formulary status Jun 08** ▪ nebivolol (Bystolic)	BCF		Pending approval	Pending approval
				Currently BCF ▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Jun 08 (update; reviewed Aug 07	Newer Antihistamines	**Recommended for non-formulary status Jun 08** ▪ levocetirizine (Xyzal)	BCF		Pending approval	Pending approval
		To remain NF ▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)		▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update; reviewed Aug 07)	Leukotriene Modifiers	**Recommended for non-formulary status Jun 08** ▪ Zileuton ER (Zyflo CR)	BCF		Pending approval	Pending approval

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To remain NF ▪ zileuton (Zyflo)		Currently BCF ▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Jun 08 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07 ▪ CCB/ARB combos Nov 07 update	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Jun 08** ▪ olmesartan/amlodipine (Azor)	BCF	-		
		To remain NF ▪ valsartan amlodipine (Exforge)			13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ **moexipril (Univasc),** ▪ **moexipril / HCTZ (Uniretic** ▪ **perindopril (Aceon)** ▪ **quinapril (Accupril)** ▪ **quinapril / HCTZ (Accuretic)** ▪ **ramipril (Altace)** ACE/CCB combos ▪ **felodipine/enalapril (Lexxel)** ▪ **verapamil/trandolapril (Tarka)** ARBs ▪ **eprosa tan (Teveten)** ▪ **eprosa tan HCTZ (Teveten HCT)** ▪ **irbesar an (Avapro)** ▪ **irbesar an HCTZ (Avalide)** ▪ **olmesa tan (Benicar)** ▪ **olmesa tan HCTZ (Benicar HCT)** ▪ **valsart n (Diovan)** ▪ **valsart n HCTZ (Diovan HCT)**		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ **15 Feb 06** ACE/CCB combos ▪ **26 Jul 06** ARBs ▪ **21 Nov 07**
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uro tral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)
Nov 07 (update, original review Aug 05)	Calcium Channel Blockers	**Currently non-formulary, recommended for UF status Nov 07** ▪ amlodipine (Norvasc generic)	BCF	**Recommended for addition to BCF Nov 07** ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To Remain Non-Formulary ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently on the BCF ▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF		13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ **mixed amphetamine salts ER (Adderall XR)** ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF		13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ **EE 30 mcg** / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Leukotriene Modifiers	▪ zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
Aug 07 (new drug update, original review Nov 05)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended for non-formulary status Aug 07 ▪ fluticasone furoate (Veramyst)			17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics		BCF	▪ temazepam 15 and 30 mg	17 Jan 07	
Aug 06	TZDs		BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	
Aug 06	H2 Antagonists / GI protectants		BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended for non-formulary status Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 05	MS-DMDs		ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle
ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE5 Inhibitors = Phosphodiesterase- type 5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs= Thiazolidinediones
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix D – Table of Abbreviations

ABA	Adrenergic Beta Antagonist drug class
AE	adverse event
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BMD	bone mineral density
BP	blood pressure
CCB	calcium channel blocker
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CMA	cost minimization analysis
CR	controlled release (extended release)
DHP	dihydropyridine
DoD	Department of Defense
CI	confidence interval
ED	erectile dysfunction
FCP	Federal Ceiling Price
FDA	Food and Drug Administration
FY	fiscal year
GA	Glaucoma Agent drug class
HA	Health Affairs
HCTZ	hydrochlorothiazide
HDL	high density lipoprotein cholesterol
IDD-P	Insoluble drug delivery microparticle
IR	immediate release
IU	international unit
JIA	juvenile idiopathic arthritis
LDL	low density lipoprotein cholesterol
LIP-1s	Antilipidemic -1 drug class
LIP-2s	Antilipidemic -2 drug class
LM	Leukotriene Modifier drug class
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
OR	odds ratio
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE5	phosphodiesterase type 5
PEC	Pharmacoeconomic Center
PORT	Pharmaceutical Outcomes Research Team
PTH	parathyroid hormone
QD	once daily
QL	quantity limit
SERM	selective estrogen receptor modulator
TC	total cholesterol
T2DM	Type 2 diabetes mellitus
TMA	TRICARE Management Activity
UF VARR	Uniform Formulary Voluntary Agreement for Retail Refund

DECISION PAPER
DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
February 2008

1) CONVENING

2) ATTENDANCE

3) REVIEW MINUTES OF LAST MEETING

4) ITEMS FOR INFORMATION

A. National Defense Authorization Act (NDAA) 2008 Sec. 703. Inclusion of TRICARE Retail Pharmacy Program In Federal Procurement Of Pharmaceuticals - LTC Kelly provided the P&T Committee an overview of NDAA 2008 Sec. 703, which addresses the inclusion of TRICARE Retail Pharmacy Program (TRRx) in Federal Procurement of Pharmaceuticals. This law requires that "any prescription filled on or after the date of the enactment of the National Defense Authorization Act for Fiscal Year 2008, the TRICARE retail pharmacy program shall be treated as an element of the Department of Defense for purposes of the procurement of drugs by Federal agencies under section 8126 of title 38 to the extent necessary to ensure that pharmaceuticals paid for by the Department of Defense that are provided by pharmacies under the program to eligible covered beneficiaries under this section are subject to the pricing standards in such section 8126.'' The presentation included: 1) NDAA 2008 Section 703 background; 2) a description and estimate of Federal Ceiling Price (FCP) relative to other prices paid by DoD to manufacturers for brand-name medications; 3) the evolution of FCP in the TRRx; and 4) formulary management strategy going forward in light of NDAA 2008 Section 703 legislation.

B. Outcomes Research Initiatives – Lt Col Bacon briefed the P&T Committee on the establishment of an Outcomes Research Team, the Team's objectives, ongoing research projects, and potential outcomes research initiatives.

C. Re-Evaluation of Quinapril and Quinapril/Hydrochlorothiazide(HCTZ)'s UF Status

The P&T Committee re-evaluated the UF status of quinapril (Accupril) and quinapril/HCTZ (Accuretic), in light of recent price reductions in the generic formulations across all three points of service. This marked the first re-evaluation of a non-formulary agent for 1st tier UF status using the P&T Committee's process for the re-evaluation of non-formulary agents, which was established at the May 2007 meeting and approved by the Director, TMA on 24 June 2007. The Pharmacoeconomic Center (PEC) identified quinapril and quinapril/HCTZ as candidates for UF consideration upon application of the process criteria to the approved list of non-formulary drug agents for re-evaluation of UF status (See Table 1).

Clinical Effectiveness Conclusion - At the August 2005 P&T Committee meeting, the Committee concluded that, in general, quinapril and quinapril/HCTZ had similar clinical effectiveness relative to other angiotensin converting enzyme (ACE) inhibitors in regards to efficacy, safety, tolerability, and clinical outcomes.

Cost Effectiveness Conclusion – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) that quinapril and quinapril/HCTZ have similar cost-effectiveness relative to the other UF ACE inhibitors.

COMMITTEE ACTION: UF DECISION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ACE inhibitor and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, and 4 absent) that quinapril and quinapril/HCTZ be immediately reclassified as generic on the UF. (See paragraph 4E on page 9 of the P&T Committee minutes). This agent was on the "list of non-formulary drugs for re-evaluation of UF status" presented to the BAP in January 2008 and approved by Director, TMA on 13 February 2008. As such, no further approval is needed.

5) REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on one new drug recently approved by the FDA (see Appendix B). The P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status. Therefore, UF consideration was deferred until the drug class review is completed. The P&T Committee discussed the need for a days supply quantity limit (QL) (no multiple fills for multiple co-pays) for sapropterin tablets (Kuvan) based on dosing and laboratory monitoring recommendations in the package insert.

COMMITTEE ACTION: QL – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) to recommend a QL for sapropterin tablets of a 45 days supply in the TRICARE Mail Order Pharmacy Program (TMOP) and a 30 days supply in the TRRx (no multiple fills for multiple co-pays). (See paragraph 5A on page 10 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Recently Approved Agents in Classes Previously Reviewed for the UF

The Committee was briefed on newly approved drugs that fall into classes previously reviewed for the UF. The clinical and economic analyses of these classes will be completed for a future meeting. The Committee took no action.

6) UTILIZATION MANAGEMENT – PRIOR AUTHORIZATIONS (PAs)/(QLs)/ MEDICAL NECESSITY (MNs)

A. Renin-Angiotensin Antihypertensives (RAAs) – Valsartan MN Criteria – The Committee discussed the MN criteria for valsartan with regard to a new FDA-approved indication for use for pediatric hypertension. The Angiotensin Receptor Blocker (ARB) drug class was previously reviewed for UF placement in May 2007. At the time of the meeting, losartan (Cozaar) was the only FDA-approved ARB for treating hypertension in children aged 6 – 16 years of age. Valsartan (Diovan) is now FDA-approved for treating children aged 6 – 16 years with hypertension; it is not approved for treating children with heart failure. FDA approval for valsartan was based on a study in 261 children with hypertension who received valsartan for two weeks. At the end of the two week study period, valsartan treatment resulted in statistically significant reductions in both systolic and diastolic blood pressure.

The Committee recommended that MN be approved for children between the ages of 6 and 16 years who have failed to respond adequately to treatment with losartan or who have experienced adverse effects to losartan.

COMMITTEE ACTION: The P&T Committee voted (9 for, 3 opposed, 1 abstained, 4 absent) to approve the MN criteria for valsartan. (See paragraph 6A on page 11 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Targeted Immunomodulatory Biologics (TIBs)

1) Administrative Action - PA for Adalimumab (Humira)

At the November 2007 DoD P&T committee meeting, adalimumab (Humira) was chosen as the Extended Core Formulary (ECF) agent, as it was the most cost effective TIB with multiple FDA-approved indications. Alefacept (Amevive) and efalizumab (Raptiva) were placed on the UF. Etanercept (Enbrel), the other multi-indication TIB, was made non-formulary along with anakinra (Kineret). Infliximab (Remicade), abatacept (Orencia), and rituximab (Rituxan) were not affected by the UF decision, since these medications fall under the TMA medical benefit and are not part of the pharmacy benefit, given their route of intravenous (IV) administration. The TIB UF decisions have a scheduled implementation date of June 18th 2008.

In January 2008, the FDA approved Humira for treatment of plaque psoriasis. At the time of the November 2007 Committee meeting, Humira was FDA-approved for rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and Crohn's disease (adults). Enbrel is FDA-approved for RA, juvenile RA, AS, PsA, and plaque psoriasis.

The FDA approved Humira's indication for plaque psoriasis based on two recently published clinical trials; the CHAMPION trial, published in December 2007, and Menter, et al published in January 2008. The CHAMPION trial was a randomized, placebo- and methotrexate-controlled trial in 261 patients with mild to moderate plaque psoriasis. The primary endpoint was Psoriasis Areas and

Severity Index (PASI) 75% response. At the end of 16 weeks, 79.6% of Humira-treated patients achieved a PASI 75 response, compared to only 35.5% and 18.9% of the methotrexate- and placebo-treated patients, respectively.

The Menter et al study included 1,212 patients with moderate to severe psoriasis randomized to receive either Humira or placebo for an initial 16 week double-blinded treatment phase. At the end of that period, 71% of Humira-treated patients achieved a PASI 75% response, compared to 7% of placebo-treated patients. With regard to safety and tolerability, both studies demonstrated a similar safety profile to that established in previous Humira clinical trials.

The FDA-approved plaque psoriasis indication will be added to the PA for Humira.

2) *QL for TIBs*

Currently, quantity and/or days supply limits apply to Enbrel (etanercept), Humira (adalimumab), and Kineret (anakinra), as outlined in Appendix C. In general, patients are limited to a 4-week supply of these medications at retail network pharmacies at any one time with no multiple fills for multiple copays. Patients are slso limited to a 6- to 8-week supply at the TMOP, based on product labeling and packaging. The intent of the QL is to limit potential wastage in the event medications are discontinued or changed.

A change in the QLs for the TIBs was recommended to establish consistent and uniform amounts supplied in the TRRx and TMOP points of service across the drug class. Currently only Enbrel, Humira and Kineret have QLs at TRRx and TMOP. A four-week supply for Enbrel and Humira is allowed at the TRRx, with a six week supply allowed in the TMOP. However, for Kineret, an 8 week supply is allowed at TMOP. A change in the QL was proposed to allow a QL for Humira, Amevive, Raptiva, Enbrel, and Kineret of four weeks supplied at TRRX. In the TMOP, the proposal was a QL for Humira, Raptiva, Enbrel and Kineret of an 8 week supply. No QL is proposed for Amevive in the TMOP, since it is not supplied through that point of service. The number of syringes/vials supplied under these limits is reflected in Table 2.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) to approve the QLs outlined above in Table 2 to allow adalimumab (Humira), etanercept (Enbrel), and anakinra (Kineret) a four weeks supply via TRRx and 8 weeks supply via TMOP. The Committee voted to add the same limits to efalizumab (Raptiva). A four weeks supply limit was agreed for Alefacept (Amevive) at TRRx, with no QL in the TMOP, as Amevive is not available through the TMOP. (See paragraph 6B on page 12 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7) BCF / ECF REVIEW

A. Clarification of Basic Core Formulary (BCF) Listing - As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in four BCF drug classes: antibiotics (nitrofurantoin monohydrate/macrocrystals [MacroBid]), proton pump inhibitors (esomeprazole [Nexium] powder packets), cough and cold preparations (chlorpheniramine 8 mg/pseudoephedrine 120 mg sustained release [Deconamine SR]), and miscellaneous migraine medications (isometheptene 65 mg/dichloralphenazone 100 mg/ acetaminophen 325 mg [Midrin]).

COMMITTEE ACTION: The P&T Committee recommended (votes on Table 3) the following changes to the current BCF drug classes as outlined in Table 3. (See paragraph 7 on page 13 of the P&T Committee minutes and Appendix D on page 24).

Table 3 - Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Antibiotics	Nitrofurantoin macrocrystals oral (Does not include MacroBid)	Clarify BCF listing to: "Nitrofurantoin oral (50 mg macrocrystals, 100 mg monohydrate/macrocrystals)"	13	0	0	4
Cough and Cold Preparations	Chlorpheniramine 8 mg / pseudoephedrine 120 mg sustained release (Deconamine SR)	Remove BCF listing: "Chlorpheniramine 8 mg / pseudoephedrine 120 mg sustained release" (specific brand name is Deconamine SR)	13	0	0	4
Miscellaneous Migraine Medications	Isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg (Midrin)	Remove BCF listing:" Isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg" (specific brand name is Midrin)	10	3	0	4
Proton Pump Inhibitors	Esomeprazole (Nexium)	Clarify BCF listing to: "esomeprazole (Nexium) 20 and 40 mg capsule"	13	0	0	4

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Administrative Action - The PEC obtained recommendations from members of the P&T Committee regarding clarification of the BCF listing for the following medications: antibiotics (amoxicillin oral, doxycycline oral, and cephalexin oral), antifungals (nystatin oral), inhaled asthma agents (albuterol oral inhaler), contraceptives, miscellaneous respiratory medications (insect allergy kits), and ophthalmic antibiotics and combinations (sulfacetamide sodium 10% ophthalmic ointment). Administrative changes will include removal of obsolete medications and more comprehensive delineation of BCF listings. (See Appendix D on page 24 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8) UPDATE ON SIMVASTATIN/EZETIMIBE – ENHANCE STUDY

The P&T Committee was briefed on the "effect of combination ezetimibe and high-dose simvastatin vs. simvastatin alone on the atherosclerotic process in subjects with heterozygous familial hypercholesterolemia" (ENHANCE) study. The ENHANCE study compared simvastatin/ezetimibe (Vytorin) 80/10 mg with simvastatin 80 mg in patients with heterozygous familial hypercholesterolemia who had baseline low-density lipoprotein levels exceeding 300 mg/dL. The primary endpoint of the trial was the change in carotid intima media thickness (CIMT). The trial did not evaluate clinical outcomes (e.g., mortality, myocardial infarction). There was no significant difference between the two groups with regard to changes in CIMT. Three ongoing studies are addressing outcomes with simvastatin/ezetimibe. No action necessary.

Appendix A – Implementation Status of UF Recommendations / Decisions

Appendix B – Newly Approved Drugs

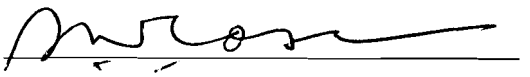
Appendix C – Existing Quantity Limits and Recommended QLs for TIBS

Appendix D – BCF/ECF Review

Appendix E – Table of Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.



S. Ward Casscells, III, M.D.

Department of Defense
Pharmacy and Therapeutics Committee Minutes
February 2008

1) CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 1000 (EST) hours on 13 Feb 2008 via a teleconference hosted by the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2) ATTENDANCE

A. Voting Members Present

Col John Kugler, MC, USA	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Col Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Walter Downs, MC *for* LCDR Michelle Perelló, MC	Navy, Internal Medicine Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
Col Karl R. Kerchief, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC (P) Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer

B. Voting Members Absent

Major William Hannah, MC	Air Force, Internal Medicine Physician
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LCDR Scott Akins, MC	Navy, Pediatrics Physician
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Deputy General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plan Operations, TMA

E. Others Present

CDR Matthew Carlberg, MC, USN	DoD PEC
Lt Col James McCrary, MC, USAF	DoD PEC
LTC Chris Conrad, MC, USA	DoD PEC
Maj Wade Tiller, BSC, USAF	DoD PEC
Maj Josh Devine, BSC, USAF	DoD PEC
CPT Josh Napier, MC, USA	DoD PEC
Angela Allerman, Pharm.D.	DoD PEC
Julie Liss, Pharm.D.	DoD PEC
David Meade, Pharm.D.	DoD PEC
Harsha Mistry, Pharm.D.	DoD PEC
Eugene Moore, Pharm.D.	DoD PEC
Shana Trice, Pharm.D.	DoD PEC
Nancy Misel, RPh	Director, Air Force High Dollar Program
LCDR James Ellzy, MC, USN	Vice DoD P&T Committee Chair
Lt Col Thom Bacon	TMA Pharmaceutical Operations Directorate
CDR Rob Hayes	USPHS/IHS
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia
Major Mike Lee, BSC	Air Force, Alternate Pharmacist Officer
Carol Cooper	Associate General Counsel, TMA

3) REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – Nov 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of Nov Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the Nov 2007 DoD P&T Committee meeting on February 13, 2008.

4) ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. **Beneficiary Advisory Panel (BAP) Briefing** – LCDR Ellzy, Lt Col Bacon, and LTC Kelly briefed the members of the P&T Committee regarding the Nov 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. **Implementation Status of UF Decisions** – The PEC staff briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since August 2007 (Appendix A).

C. **National Defense Authorization Act (NDAA) 2008 Sec. 703. Inclusion of TRICARE Retail Pharmacy Program In Federal Procurement Of Pharmaceuticals** - LTC Kelly provided the P&T Committee an overview of NDAA 2008 Sec. 703, which addresses the inclusion of TRICARE Retail Pharmacy Program (TRRx) in Federal Procurement of Pharmaceuticals. This law requires that "any prescription filled on or after the date of the enactment of the National Defense Authorization Act for Fiscal Year 2008, the TRICARE retail pharmacy program shall be treated as an element of the Department of Defense for purposes of the procurement of drugs by Federal agencies under section 8126 of title 38 to the extent necessary to ensure that pharmaceuticals paid for by the Department of Defense that are provided by pharmacies under the program to eligible covered beneficiaries under this section are subject to the pricing standards in such section 8126." The presentation included: 1) NDAA 2008 Section 703 background; 2) a description and estimate of FCP relative to other prices paid by DoD to manufacturers for brand-name medications; 3) the evolution of FCP in the TRRx; and 4) formulary management strategy going forward in light of NDAA 2008 Section 703 legislation.

D. **Outcomes Research Initiatives** – Lt Col Bacon briefed the P&T Committee on the establishment of an Outcomes Research Team, the Team's objectives, ongoing research projects, and potential outcomes research initiatives.

E. **Re-Evaluation of Quinapril and Quinapril/Hydrochlorothiazide (HCTZ)'s UF Status**

The P&T Committee re-evaluated the UF status of quinapril (Accupril) and quinapril/HCTZ (Accuretic), in light of recent price reductions in the generic formulations across all three points of service. This marked the first re-evaluation of a non-formulary agent for 1st tier UF status using the P&T Committee's process for the re-evaluation of non-formulary agents, which was established at the May 2007 meeting and approved by the Director, TMA on 24 June 2007. The PEC identified quinapril and quinapril/HCTZ as candidates for UF consideration upon application of the process criteria to the approved list of non-formulary drug agents for re-evaluation of UF status (Table 1).

Table 1 – Non-Formulary Agents for Re-Evaluation

Generic Name	Brand Name	UF Class	Generics Shipping
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
ramipril	Altace	ACEs	N
quinapril, quinapril/HCTZ	Accupril, Accuretic	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan /Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N

Clinical Effectiveness Conclusion - At the August 2005 P&T Committee meeting, the Committee concluded that, in general, quinapril and quinapril/HCTZ had similar clinical effectiveness relative to other angiotensin converting enzyme (ACE) inhibitors in regards to efficacy, safety, tolerability, and clinical outcomes.

Cost Effectiveness Conclusion – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) that quinapril and quinapril/HCTZ have similar cost-effectiveness relative to the other UF ACE inhibitors.

COMMITTEE ACTION: UF DECISION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ACE inhibitor and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 0 abstained, and 4 absent) that quinapril and quinapril/HCTZ be immediately reclassified as generic on the UF.

5) REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on one new drug recently approved by the FDA (see Appendix B). The P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status. Therefore, UF consideration

was deferred until the drug class review is completed. The P&T Committee discussed the need for a days supply quantity limit (QL) (no multiple fills for multiple co-pays) for sapropterin tablets (Kuvan) based on dosing and laboratory monitoring recommendations in the package insert.

COMMITTEE ACTION: QL – The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) to recommend a QL for sapropterin tablets of a 45 days supply in the TRICARE Mail Order Pharamcy Program (TMOP) and a 30 days supply in the TRRx (no multiple fills for multiple co-pays).

B. Recently Approved Agents in Classes Previously Reviewed for the UF

The Committee was briefed on newly approved drugs that fall into classes previously reviewed for the UF. The clinical and economic analyses of these classes will be completed for a future meeting. The Committee took no action.

6) UTILIZATION MANAGEMENT – PRIOR AUTHORIZATIONS (PAs)/(QLs)/ MEDICAL NECESSITY (MNs)

A. Renin-Angiotensin Antihypertensives (RAAs) – Valsartan MN Criteria – The Committee discussed the MN criteria for valsartan with regard to a new FDA-approved indication for use for pediatric hypertension. The Angiotensin Receptor Blocker (ARB) drug class was previously reviewed for UF placement in May 2007. At the time of the meeting, losartan (Cozaar) was the only FDA-approved ARB for treating hypertension in children aged 6 – 16 years of age. Valsartan (Diovan) is now FDA-approved for treating children aged 6 – 16 years with hypertension; it is not approved for treating children with heart failure. FDA approval for valsartan was based on a study in 261 children with hypertension who received valsartan for two weeks. At the end of the two week study period, valsartan treatment resulted in statistically significant reductions in both systolic and diastolic blood pressure.

The Committee recommended that MN be approved for children between the ages of 6 and 16 years who have failed to respond adequately to treatment with losartan or who have experienced adverse effects to losartan.

COMMITTEE ACTION: The P&T Committee voted (9 for, 3 opposed, 1 abstained, 4 absent) to approve the MN criteria for valsartan.

B. Targeted Immunomodulatory Biologics (TIBs)

1) Administrative Action - PA for Adalimumab (Humira)

At the November 2007 DoD P&T committee meeting, adalimumab (Humira) was chosen as the Extended Core Formulary (ECF) agent, as it was the most cost effective TIB with multiple FDA-approved indications. Alefacept (Amevive) and efalizumab (Raptiva) were placed on the UF. Etanercept (Enbrel), the other multi-indication TIB, was made non-formulary along with anakinra (Kineret). Infliximab (Remicade), abatacept (Orencia), and rituximab (Rituxan) were not affected by the UF decision, since these medications fall under the TMA medical benefit and are not part of the pharmacy benefit, given their route of intravenous (IV) administration. The TIB UF decisions have a scheduled implementation date of June 18th 2008.

In January 2008, the FDA approved Humira the treatment of plaque psoriasis. At the time of the November 2007 Committee meeting, Humira was FDA-approved for rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and Crohn's disease (adults). Enbrel is FDA-approved for RA, juvenile RA, AS, PsA, and plaque psoriasis.

The FDA approved Humira's indication for plaque psoriasis based on two recently published clinical trials; the CHAMPION trial, published in December 2007, and Menter, et al published in January 2008. The CHAMPION trial was a randomized, placebo- and methotrexate-controlled trial in 261 patients with mild to moderate plaque psoriasis. The primary endpoint was Psoriasis Areas and Severity Index (PASI) 75% response. At the end of 16 weeks, 79.6% of Humira-treated patients achieved a PASI 75 response, compared to only 35.5% and 18.9% of the methotrexate- and placebo-treated patients, respectively.

The Menter et al study included 1,212 patients with moderate to severe psoriasis randomized to receive either Humira or placebo for an initial 16 week double-blinded treatment phase. At the end of that period, 71% of Humira-treated patients achieved a PASI 75% response, compared to 7% of placebo-treated patients. With regard to safety and tolerability, both studies demonstrated a similar safety profile to that established in previous Humira clinical trials.

The FDA-approved plaque psoriasis indication will be added to the PA for Humira.

2) *QL for TIBs*

Currently, quantity and/or days supply limits apply to Enbrel (etanercept), Humira (adalimumab), and Kineret (anakinra), as outlined in Appendix C. In general, patients are limited to a 4-week supply of these medications at retail network pharmacies at any one time withno multiple fills for multiple copays. Patients are also limited to a 6- to 8-week supply at the TMOP, based on product labeling and packaging. The intent of the QL is to limit potential wastage in the event medications are discontinued or changed.

A change in the QLs for the TIBs was recommended to establish consistent and uniform amounts supplied in the TRRx and TMOP points of service across the drug class. Currently only Enbrel, Humira and Kineret have QLs at TRRx and TMOP. A four-week supply for Enbrel and Humira is allowed at the TRRx, with a six week supply allowed in the TMOP. However, for Kineret, an 8 week supply is allowed at TMOP. A change in the QL was proposed to allow a QL for Humira, Amevive, Raptiva, Enbrel, and Kineret of four weeks supplied at TRRX. In the TMOP, the proposal was a QL for Humira, Raptiva, Enbrel and Kineret of an 8 week supply. No QL is proposed for Amevive in the TMOP, since it is not supplied through that point of service. The number of syringes/vials supplied under these limits is reflected in Table 2.

Table 2 - Recommended Maximum Quantities Dispensed at One Time: TIBs

Point of Service / Notes	Adalimumab (Humira)	Etanercept (Enbrel)	Anakinra (Kineret)	Alefacept (Amevive)	Efalizumab (Raptiva)
Retail Network	4 wks supply (2 packs of 2 syringes)	4 wks supply (based on instructions for use)	4 wks supply (1 pack of 28 syringes)	4 wks supply (1 pack 4 syringes)	4 wks supply (based on instructions for use)
TMOP	8 wks supply (4 packs of 2 syringes)	8 wks supply (based on instructions for use)	8 wks supply (2 packs of 28 syringes)	Not supplied through TMOP	8 wks supply (based on instructions for use)
Other Issues	Crohn's disease starter pack includes 6 pens for 1st 4 wks, no refills	--	--	--	Not to exceed 200 mg/week 8 vials/ 4 wks 16 vials/ 8 wks

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 0 abstained, 4 absent) to approve the QLs outlined above in Table 2 to allow adalimumab (Humira), etanercept (Enbrel), and anakinra (Kineret) a four weeks supply via TRRx and 8 weeks supply via TMOP. The Committee voted to add the same limits to efalizumab (Raptiva). A four weeks supply limit was agreed for Alefacept (Amevive) at TRRx, with no QL in the TMOP, as Amevive is not available through the TMOP.

7) BCF / ECF REVIEW

A. Clarification of Basic Core Formulary (BCF) Listing - As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in four BCF drug classes: antibiotics (nitrofurantoin monohydrate/macrocrystals [MacroBid]), proton pump inhibitors (esomeprazole [Nexium] powder packets), cough and cold preparations (chlorpheniramine 8 mg/pseudoephedrine 120 mg sustained release [Deconamine SR]), and miscellaneous migraine medications (isometheptene 65 mg/dichloralphenazone 100 mg/ acetaminophen 325 mg [Midrin]).

Esomeprazole powder packets were determined to not be cost-effective, thus the current BCF listing for esomeprazole was revised to specifically include only the 20 and 40 mg capsules. Chlorpheniramine 8 mg/pseudoephedrine 120 mg SR (Deconamine SR) was removed from the BCF due to availability issues from the wholesaler, resulting in low utilization (less than 300 prescriptions dispensed monthly at the MTFs). Midrin was also removed from the BCF due to ongoing shortages which will likely persist due in part to the FDA's campaign to halt the manufacturing of unapproved products containing ergotamine. The BCF listing for nitrofurantoin was revised to include nitrofurantoin monohydrate/macrocrystals (MacroBid), due to availability of cost-effective generic products, and decreasing availability of nitrofurantoin macrocrystals (Macrodantin). Details are outlined in Appendix D.

COMMITTEE ACTION: The P&T Committee recommended the following changes to the current BCF drug classes as outlined in Table 3. (See Appendix D for rationale).

Table 3 - Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Antibiotics	Nitrofurantoin macrocrystals oral (Does not include MacroBid)	Clarify BCF listing to: "Nitrofurantoin oral (50 mg macrocrystals, 100 mg monohydrate/macrocrystals)"	13	0	0	4
Cough and Cold Preparations	Chlorpheniramine 8 mg / pseudoephedrine 120 mg sustained release (Deconamine SR)	Remove BCF listing: "Chlorpheniramine 8 mg / pseudoephedrine 120 mg sustained release" (specific brand name is Deconamine SR)	13	0	0	4
Miscellaneous Migraine Medications	Isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg (Midrin)	Remove BCF listing:" Isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg" (specific brand name is Midrin)	10	3	0	4
Proton Pump Inhibitors	Esomeprazole (Nexium)	Clarify BCF listing to: "esomeprazole (Nexium) 20 and 40 mg capsule"	13	0	0	4

B. Administrative Action - The PEC obtained recommendations from members of the P&T Committee regarding clarification of the BCF listing for the following medications: antibiotics (amoxicillin oral, doxycycline oral, and cephalexin oral), antifungals (nystatin oral), inhaled asthma agents (albuterol oral inhaler), contraceptives, miscellaneous respiratory medications (insect allergy kits), and ophthalmic antibiotics and combinations (sulfacetamide sodium 10% ophthalmic ointment). Administrative changes will include removal of obsolete medications and more comprehensive delineation of BCF listings. Details are outlined in Appendix D.

8) UPDATE ON SIMVASTATIN/EZETIMIBE – ENHANCE STUDY

The P&T Committee was briefed on the "effect of combination ezetimibe and high-dose simvastatin vs. simvastatin alone on the atherosclerotic process in subjects with heterozygous familial hypercholesterolemia" (ENHANCE) study. The ENHANCE study compared simvastatin/ezetimibe (Vytorin) 80/10 mg with simvastatin 80 mg in patients with heterozygous familial hypercholesterolemia who had baseline low-density lipoprotein levels exceeding 300 mg/dL. The primary endpoint of the trial was change in carotid intima media thickness (CIMT); clinical outcomes (e.g., mortality, myocardial infarction) were not evaluated. There was no significant difference between the two groups with regard to changes in CIMT. Three ongoing studies are addressing outcomes with simvastatin/ezetimibe. No action necessary.

9) ADJOURNMENT

The meeting adjourned at 1330 hours on 13 Feb 2008. The next meeting will be 12-13 June 2008.

John Kugler, M.D.
Colonel, Medical Corps, U.S. Army
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	13 Feb 08	18 Jun 08 (120 days)
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin tablets (Uroxatral)	13 Feb 08	16 Apr 08 (60 days)
Nov 07	Adrenergic Beta-Blocking Agents	-	BCF	▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	13 Feb 08	-
Nov 07 (update, original review Aug 05)	Calcium Channel Blockers	**Currently non-formulary, recommended for UF status Nov 07** ▪ amlodipine (Norvasc generic)	BCF	**Recommended for addition to BCF Nov 07** ▪ amlodipine besylate tablets	13 Feb 08	13 Feb 08
		To Remain Non-Formulary ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently on the BCF ▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	-	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	-	13 Feb 08	16 Apr 08 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Lutera, Sronyx, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Nov 07 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Nov 07** ▪ valsartan/amlodipine (Exforge)	BCF	-	13 Feb 08	16 Apr 08 (60 days)
		To remain NF ACE inhibitors ▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Leukotriene Modifiers	▪ zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
Aug 07 (new drug update, original review Nov 05)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended for non-formulary status Aug 07 ▪ fluticasone furoate (Veramyst)			17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (updated Nov 07)	ADHD / Narcolepsy Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	-
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated Nov 06, Nov 07)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended for non-formulary status Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)		-	17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05 (re-review Nov 07)	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05 (updated Nov 07)	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		Recommended for non-formulary status Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle
ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs= Thiazolidinediones
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. February 2008 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Sapropterin dihydrochloride tablets (Kuvan, BioMarin Pharmaceutical) Synthetic tetrahydrobiopterin, the enzyme cofactor for phenylalanine hydroxylase	Dec 07 To reduce blood phenylalanine levels in patients with hyperphenylalanemia due to tetrahydrobiopterin-responsive phenylketonuria. Kuvan is to be used in conjunction with a phenylalanine-restricted diet.	No UF recommendation at this meeting. Consideration of UF status deferred until prescription metabolic and vitamin drugs are reviewed; UF review not anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit of 45 days ▪ Retail Network o Days supply limit of 30 days

Appendix C – Existing Quantity Limits and Recommended QLs for Targeted Immunomodulatory Biologics

Quantity Limits	Adalimumab (Humira)	Etanercept (Enbrel)	Anakinra (Kineret)	Alefacept (Amevive)	Efalizumab (Raptiva)
Current Retail Network	Maximum quantity dispensed at any one time is 4 weeks supply (2 packs of 2 syringes). Does not apply to the Crohn's Disease starter pack (6 pens for the first 4 weeks of treatment), which is limited to 1 package (6 pens), with no refills.	4-week supply week supply in mail order (based on instructions for use on the prescription)	Maximum quantity dispensed at any one time is 4 weeks supply (1 package of 28 syringes) in retail	No current QL	No current QL
Current TMOP	Maximum quantity dispensed at any one time is 4 weeks supply (3 packs of 2 syringes). Does not apply to the Crohn's Disease starter pack (6 pens for the first 4 weeks of treatment), which is limited to 1 package (6 pens), with no refills.	6-week supply (based on instructions for use on the prescription)	Maximum quantity dispensed at any one time is 8 weeks supply (2 packages of 28 syringes)	Not supplied through TMOP	No current QL
Recommended Retail Network	4 wks supply (2 packs of 2 syringes)	4 wks supply (based on instructions for use)	4 wks supply (1 pack of 28 syringes)	4 wks supply (1 pack 4 syringes)	4 wks supply (based on instructions for use)
Recommended TMOP	8 wks supply (4 packs of 2 syringes)	8 wks supply (based on instructions for use)	8 wks supply (2 packs of 28 syringes)	Not supplied through TMOP	8 wks supply (based on instructions for use)
Other Issues	Crohn's disease starter pack includes 6 pens for first 4 wks, no refills	Not applicable	Not applicable	Not applicable	Not to exceed 200 mg/week 8 vials/ 4 wks 16 vials/ 8 wks

Appendix D– Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF listing	Recommended Action / Administrative Action

Antibiotics	Amoxicillin oral	• The current BCF listing does not clarify strengths and dosage forms.
		• Approximately 90% of MTF utilization is for the following strengths:
		  • 250 mg and 500 mg capsules
		  • 250/5 mL and 400mg/5 mL suspension
		• Administrative:
		  • Clarify BCF listing: "Amoxicillin oral (250 mg and 500 mg capsules; 250/5 mL and 400 mg/5mL suspension)"

Antibiotics	Cephalexin oral	• The current BCF listing does not clarify strengths and dosage forms.
		• Approximately 90% of MTF utilization data is for the following strengths:
		  • 250 mg and 500 mg capsules
		  • 250/5 mL suspension
		• Administrative:
		  • Clarify BCF listing: "Cephalexin oral (250 mg and 500 mg capsules; 250/5 mL suspension)"

Antibiotics	Doxycycline oral (Does not include Periostat)	• In Jun 2001 the BCF was clarified to exclude doxycycline 20 mg (Periostat), due to its mechanism in dental procedures as inhibiting collagenase, rather than antimicrobial effects.
		• In May 2006 a 40 mg formulation for rosacea (Oracea) was marketed.
		• The 100 mg strengths are used for antimicrobial effects.
		• Approximately 90% of MTF utilization data is for the following strengths:
		  • 100 mg doxycycline hyclate tablet & capsules
		• Administrative:
		  • Clarify BCF listing: "Doxycycline hyclate (100 mg tablets or capsules)"

Antibiotics	Nitrofurantoin macrocrystals oral (Does not include MacroBid)	• In Feb 2001 the BCF was clarified to exclude nitrofurantoin monohydrate/macrocrystals (MacroBid) due to cost and availability only in a proprietary formulation. • Nitrofurantoin monohydrate/macrocyrstalline (MacroBid) is now available in cost-effective generic formulations. • There are supply issues with nitrofurantoin macrocrystals (Furadantin). • A 6 month review of MTF data show that >60% of nitrofurantoin utilization is for MacroBid 100 mg. • Recommendation: • Clarify BCF listing: "Nitrofurantoin oral (50 mg macrocrystals; 100 mg monohydrate/macrocrystals)"
Antifungals	Nystatin (Does not include Mycostatin Pastilles)	• The original BCF listing for nystatin oral excluded nystatin pastilles (lozenges); the pastilles are no longer commercially available. • Administrative: • Clarify BCF listing: "Nystatin", (remove "Does not include Mycostatin Pastille")
Asthma agents, inhaled	Albuterol oral inhaler (Does not include hydrofluoralkane (HFA) products)	• The current BCF listing excludes hydrofluoralkane (HFA)-containing products. Chlorofluorocarbon (CFC)-containing albuterol inhalers will be discontinued in Dec 2008 as per an FDA Final Rule. • Most manufactures have already converted to hydrofluoralkane (HFA) as the most common propellant. • Administrative: • Clarify BCF listing: "remove (Does not include HFA products)"

Drug Class or Potential Drug Class	BCF listing	Recommended Action / Administrative Action
Contraceptives	Monophasics with 30 mcg EE; 0.15 mg levonorgestrel (Nordette or equivalent; excludes Seasonale) Monophasics with 20 mcg EE; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)	• Proprietary formulations of monophasic contraceptives with 20 mcg ethinyl estradiol (EE) / 0.15 mg levonorgestrel (Allesse, Levlite) and 30 mcg EE / 0.1 mg levonorgestrel (Levlin) are no longer available. • There are continuing changes in the availability of branded generics, generics, and proprietary contraceptives. • Administrative: • Clarify BCF listing: "Specify hormonal content only, remove reference to product name unless designated non-formulary"
Cough and Cold Preparations	Chlorpheniramine 8 mg / pseudoephedrine 120 mg sustained release (Deconamine SR)	• There are availability issues with Deconamine SR which are not expected to resolve. • Currently there is low utilization of Deconamine SR with fewer than 300 Rxs dispensed monthly across all MTFs. • Recommendation: • Remove BCF listing for chlorpheniramine 8 mg/ pseudoephedrine 120 mg SR.
Miscellaneous Migraine Medications	Isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg	• There are availability issues with isometheptene 65 mg / dichloralphenazone 100 mg / acetaminophen 325 mg (Midrin) which are not expected to improve, as only 2 manufacturers remain in the marketplace. • The FDA has warned several manufacturers regarding manufacturing of unapproved products containing ergotamine derivatives. • MTF utilization of Midrin dropped from 6,000 Rxs/ monthly to less than 3,000 Rxs monthly between Aug 2007 and Dec 2007, reflecting dwindling availability. • Recommendation: • Remove BCF listing
Miscellaneous Respiratory Medications	Insect Sting Kit, Injection (EpiPen is a commonly recognized brand name)	• The current BCF listing is designated as "insect sting kit" and lists one popular proprietary name. Kits containing epinephrine are used to treat multiple types of anaphylaxis (asthma, food, insects) and are called by different names. • Healthcare providers look for epinephrine (generic) or specific brand name kits (e.g., EpiPen, Twinject). • Administrative: • Clarify BCF listing: Change insect sting kit, injection to "Epinephrine auto-injection"
Ophthalmic Antibiotic and Combinations	Sulfacetamide sodium ophthalmic ointment	• The current BCF listing for sulfacetamide sodium lists both the ointment and solution. Sulfacetamide sodium ophthalmic ointment is no longer commercially available • Administrative: • Remove BCF listing: "Sulfacetamide sodium ophthalmic ointment"
Proton Pump Inhibitors	Esomeprazole (Nexium)	• May 2007 esomeprazole (Nexium) was added to the BCF. The current BCF listing does not clarify strengths or formulations. • Esomeprazole powder packets are now available, but are not cost-effective relative to the esomeprazole capsules. • Recommendation: • Clarify BCF listing: "esomeprazole (Nexium) 20 and 40 mg capsules"

Appendix E – Table of Abbreviations

ACE	angiotensin converting enzyme
AD1s	antidepressant 1 drug class
AF-DERMS	antifungal dermatologics drug class
ARB	angiotensin receptor blocker
AS	ankylosing spondylitis
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
CCB	calcium channel blocker
CFC	chlorofluorocarbon
CIMT	carotid intima-media thickness
CFR	Code of Federal Regulations
CR	controlled release (extended release)
DoD	Department of Defense
ECF	extended core formulary
EE	ethinyl estradiol
ER	extended release
FDA	Food and Drug Administration
FY	fiscal year
HCTZ	hydrochlorothiazide
HFA	hydrofluoralkane
IV	intravenous
IR	immediate release
MHS	Military Health System
MN	medical necessity
MTF	Military Treatment Facility
PA	prior authorization
PASI	Psoriasis Area and Severity Index
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
RAA	renin-angiotensin antihypertensive drug class
PsA	psoriatic arthritis
OAB	overactive bladder drug class
QL	quantity limit
RA	rheumatoid arthritis
SR	sustained release
TIB	targeted immunomodulatory biologic
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy Program
TRRx	TRICARE Retail Pharmacy Program
UF	Uniform Formulary
XL	extended release

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2007

1) **CONVENING**
2) **ATTENDANCE**
3) **REVIEW MINUTES OF LAST MEETING**
4) **ITEMS FOR INFORMATION**
5) **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Pharmacy and Therapeutics (P&T) Committee was briefed on one new drug which was approved by the Food and Drug Administration (FDA) (see Appendix B). The Department of Defense (DoD) P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status; therefore, UF consideration was deferred until the drug class review is completed. The P&T Committee discussed the need for a quantity limit (QL) for formoterol fumarate inhalation solution, based on existing QLs for other oral inhalation products and recommendations for use in product labeling. (See paragraph 5A on page 22 and Appendix B on page 73 of the P&T Committee minutes).

COMMITTEE ACTION: QL – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend a QL for formoterol fumarate inhalation solution of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Renin Angiotensin Antihypertensive (RAA) – Valsartan/Amlodipine (Exforge)

Background – Exforge is a fixed dose combination product containing valsartan (Diovan) with amlodipine (Norvasc, generics). It is the first combination product containing an ARB with a dihydropyridine (DHP) calcium channel blocker (CCB). Valsartan/amlodipine is solely indicated for treating hypertension.

Treatment with valsartan/amlodipine has been shown in two randomized trials to produce additive blood pressure (BP) lowering and superior BP control compared to placebo and the individual components administered alone. Valsartan/amlodipine showed similar BP lowering as the fixed dose combination of lisinopril/hydrochlorothiazide (HCTZ) in one trial.

The adverse event profile of valsartan/amlodipine reflects that of the individual angiotensin receptor blocker (ARB) and DHP CCB components. In clinical trials, the

incidence of peripheral edema with valsartan/amlodipine is less than that seen when amlodipine is administered alone.

Studies evaluating the effect of valsartan/amlodipine in terms of patient convenience have not been conducted. Potential benefits of fixed dose combination drugs include reduced tablet burdens, simplified medication regimens, and improved adherence.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that, while valsartan/amlodipine offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other anti-hypertensive agents included on the UF.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (13 for, 0 opposed, 3 abstained, 1 absent) that valsartan/amlodipine is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost effective relative to Exforge.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 3 abstained, 2 absent) to recommend that valsartan/amlodipine be classified as non-formulary under the UF. (See paragraph 5B, pages 22-24 of the P&T Committee minutes).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** – Based on the clinical evaluation of valsartan/amlodipine and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for valsartan/amlodipine. (See paragraph 5B, pages 24-25 of the P&T Committee minutes for the criteria).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Network Pharmacy (TRRx) programs, and at military treatment facilities (MTFs) no later than a 60-day implementation period; and 2) TMA letter to be sent to every

beneficiary affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA). (See paragraph 5B, page 25 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. Attention Deficit Hyperactivity Disorder (ADHD)/Narcolepsy Agent – Lisdexamfetamine dimesylate (Vyvanse)

Background – Lisdexamfetamine is a pro-drug that is hydrolyzed in the gastro-intestinal tract to the stimulant dextroamphetamine and the amino acid l-lysine. It is approved for treating ADHD in children 6 to 12 years of age.

Lisdexamfetamine and a current UF product, mixed amphetamine salts extended release (ER) (Adderall XR), are manufactured by the same company; generic formulations of Adderall XR are anticipated in 2009.

With regard to efficacy, there is insufficient evidence to determine if there are clinically relevant differences between lisdexamfetamine and other ADHD stimulant products. With regard to safety, there is no evidence to suggest that the adverse event profile of lisdexamfetamine differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients report appetite suppression.

Lisdexamfetamine was designed to have less potential for abuse, diversion and overdose toxicity than amphetamine, as it requires activation in the gut. Two small manufacturer-sponsored studies in drug abusers reported that the doses of lisdexamfetamine used clinically produced similar "likeability" scores as placebo. However, lisdexamfetamine is a Schedule II controlled substance.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that lisdexamfetamine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that lisdexamfetamine had similar relative cost effectiveness compared to the other UF once daily ADHD stimulants.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of lisdexamfetamine dimesylate and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstained, 2 absent) to recommend that lisdexamfetamine dimesylate be classified as non-formulary under the UF. This recommendation was primarily based upon the determination that lisdexamfetamine offers no significant, clinically meaningful therapeutic

advantage over other once daily ADHD stimulants. (See paragraph 5C on pages 25-27 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of lisdexamfetamine dimesylate and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for lisdexamfetamine dimesylate. (See paragraph 5C, page 27 of the P&T Committee minutes for the criteria).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and at MTFs no later than a 60- day implementation period; and 2) TMA letter to be sent to every beneficiary affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5C, pages 27-28 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. Contraceptive – Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)

Background – Ethinyl estradiol (EE) 20 mcg/levonorgestrel 90 mg is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis. Four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel are included on the Basic Core Formulary (BCF). The EE 20 mcg/levonorgestrel 0.09 mg product cannot be exactly duplicated by using conventional packages of EE 20 mcg/ levonorgestrel 0.1 mg or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however, this difference in the progestin content is of questionable clinical relevance.

With respect to efficacy, there is no evidence to suggest that EE 20 mcg/ levonorgestrel 0.09 mg would differ from other similar contraceptives containing low-dose estrogen. With respect to safety, as with other continuous regimens, break-through bleeding is common with EE 20 mcg/levonorgestrel 0.09 mg, but decreases over time.

Relative Clinical Effectiveness Conclusion – The Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) that EE 20 mcg/levonorgestrel 0.09 mg did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 1 opposed, 0 abstained, 3 absent) that the weighted average cost per day of treatment for EE 20 mcg/levonorgestrel 0.09 mg is significantly higher than other UF monophasic 20 mcg EE agents used on a continuous cycle basis.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of EE 20 mcg/levonorgestrel 0.09 mg and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that Lybrel be designated as non-formulary under the UF. (See paragraph 5D, page 29 of the P&T Committee minutes).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of EE 20 mcg/levonorgestrel 0.09 mg and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for Lybrel. (See paragraph 5D, pages 29-30 of the P&T Committee minutes for the criteria).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

   COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (12 for, 2 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and no later than a 60-day implementation period at MTFs; and 2) TMA letter to be sent to every beneficiary affected by this UF decision. The implementation period will begin immediately following approval by Director, TMA. (See paragraph 5D, page 30 of the P&T Committee minutes.)

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

6) DRUG CLASS REVIEW – ADRENERGIC BETA-BLOCKING AGENTS (ABAs)

The P&T Committee evaluated the relative clinical effectiveness of the 22 ABAs marketed in the US (see Table 1). The ABA drug class was subdivided into three categories: ABAs evaluated (but not necessarily FDA-approved) for treating chronic heart failure (HF); ABAs not evaluated for HF (older ABAs used primarily for hypertension); and ABA/diuretic combinations (one combination product, timolol/ hydrochlorothiazide (HCTZ), has now been discontinued). The current BCF ABAs are metoprolol tartrate and atenolol.

The ABAs are all available in generic formulations, with the exception of carvedilol ER (Coreg CR), which was introduced to the market in March 2007. Generic formulations of carvedilol immediate release (IR) and metoprolol succinate ER were launched in mid- to late-2007.

Expenditures for the ABAs exceeded $140 million in FY 07, ranking them in the top 15 drug class expenditures for the Military Health System (MHS). In terms of 30-day equivalent prescriptions dispensed in FY 07, atenolol is the highest utilized ABA in the MHS (~225,000/month), followed by branded metoprolol succinate ER, and metoprolol tartrate (~100,000/month). Generic formulations of metoprolol succinate ER have exceeded 50,000 30-day equivalent prescriptions since August 2007. Since market introduction, carvedilol ER has seen a steady increase in utilization, which exceeded 12,000 30-day equivalent prescriptions dispensed in October 2007.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusion:

a) Labetolol was not clinically comparable to carvedilol, despite exhibiting alpha blocking properties, as it has not been evaluated for chronic HF.

b) Sotalol was not clinically comparable to the other ABAs, as it is not FDA-approved for treating chronic HF.

c) For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect.

d) For treating chronic HF, metoprolol succinate ER, carvedilol IR and ER, and bisoprolol have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there is no data to suggest that there are differences in the reduction in mortality between carvedilol, metoprolol succinate ER, or bisoprolol.

e) Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there are clinically relevant differences in the adverse event profile between carvedilol IR and carvedilol ER.

f) Despite the convenience of once daily dosing of carvedilol ER, there is no compelling clinical evidence to suggest a benefit of carvedilol ER over carvedilol IR.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) All ABAs used primarily to treat hypertension are cost-effective, with atenolol, metoprolol tartrate, and propranolol IR being the most effective.

b) All of the ABAs with clinical evidence for heart failure are effective, with carvedilol IR being the most cost effective agent.

c) Sotalol, sotalol AF, and labetalol are cost-effective.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend the following: that atenolol, atenolol-chlorthalidone, metoprolol tartrate, metoprolol succinate ER, propranolol, propranolol/HCTZ, propranolol ER, timolol, timolol/HCTZ, bisoprolol, bisoprolol/HCTZ, nadolol, nadolol/bendroflumethiazide, acebutolol, betaxolol, penbutolol, carvedilol IR, and carvedilol ER be designated formulary on the UF. (See paragraphs 6A, 6B and 6C on pages 30-36 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that atenolol and metoprolol tartrate be maintained on the BCF, and that generic formulations of metoprolol succinate ER and carvedilol IR be added to the BCF. (See paragraph 6D on pages 36-37 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7) DRUG CLASS REVIEW – ALPHA BLOCKERS (ABs) FOR BENIGN PROSTATIC HYPERTROPHY (BPH)

The P&T Committee evaluated the relative clinical effectiveness of the ABs used for BPH currently marketed in the US. The BPH ABs comprise the non-uroselective agents terazosin and doxazosin (both available in generic formulations), and the uroselective agents alfuzosin (Uroxatral) and tamsulosin (Flomax). The BPH AB class was first reviewed by the DoD P&T Committee in August 2005.

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) Based on randomized placebo-controlled trials, terazosin, doxazosin, tamsulosin, and alfuzosin were found to produce clinically significant and comparable symptom improvements when compared to placebo.

b) Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

c) There appear to be few differences in the incidence of adverse effects with alfuzosin and tamsulosin, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are vasodilatory effects.

d) There appear to be major differences in withdrawal rates due to adverse events between non-uroselective and the uroselective agents. Withdrawal rates reported in clinical trials were low overall for alfuzosin and tamsulosin.

e) The package labeling for alfuzosin contains cautions for QT prolongation effects. The effect of tamsulosin on the QT interval has not been studied.

f) Alfuzosin is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir. Tamsulosin has potential drug interactions with cimetidine and warfarin.

g) Doxazosin should be used with caution in men with hepatic failure. Alfuzosin is contraindicated in men with moderate to severe hepatic impairment (Child-Pugh categories B and C). Tamsulosin does not require dosage adjustment in men with moderate hepatic dysfunction.

h) Package labeling for all four ABs contains information regarding the potential for IFIS. For patients receiving alfuzosin and tamsulosin consultation with an ophthalmologist is recommended prior to cataract surgery.

i) Terazosin and doxazosin have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin in terms of safety/tolerability due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective ABs.

j) Alfuzosin and tamsulosin have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of MHS BPH patients requiring an uroselective agent.

k) Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH, or for safety profiles between the uroselective ABs.

l) Based on clinical issues alone, there are no compelling reasons to classify any of the AB agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step Therapy to be the most cost effective UF scenario considered.

b) UF scenario, under condition set #2, with alfuzosin as the one uroselective agent on the UF and BCF without Step Therapy was the next most cost effective UF scenario considered. However, under this UF scenario, without Step Therapy, the weighted average cost per day of therapy increased by 53% over the most cost effective UF scenario.

c) Any condition set that included tamsulosin on the UF was more costly compared to the baseline (what DoD pays today) weighted average cost per day of therapy.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) alfuzosin be maintained as the uroselective formulary AB, and that terazosin and doxazosin be maintained as the non-uroselective formulary ABs; and; and 2) tamsulosin be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin for new patients. (See paragraphs 7A, 7B and 7C on pages 37-43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: PA CRITERIA – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that the following PA criteria should apply for tamsulosin. Coverage would be approved if a patient met any of the following criteria (See paragraph 7D on pages 43-44 of the P&T Committee minutes):

1) Automated PA criteria:

   a) The patient has received a prescription for either tamsulosin or alfuzosin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   a) The patient has tried alfuzosin and had an inadequate response or was unable to tolerate treatment due to adverse effects.

   b) Treatment with alfuzosin is contraindicated.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tamsulosin and the conditions for establishing medical necessity for a non-formulary

medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) MN criteria for tamsulosin. (See paragraph 7E on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: IMPLEMENTATION PERIOD –The P&T Committee recommended (14 for, 1 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 7F on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the AB agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry terazosin and alfuzosin. (See paragraph 7G on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8) DRUG CLASS REVIEW – TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs)

The P&T Committee evaluated the relative clinical effectiveness of the targeted immunomodulatory biologics (TIBs) currently marketed in the United States. The TIB class comprises five medications covered as part of the TRICARE pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). Three similar biologic agents are not part of the pharmacy benefit due to their intravenous (IV) route of administration. Abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). Like adalimumab and etanercept, infliximab is approved for multiple indications and in many respects directly competes with these two self-administered multiple indication agents. The IV agents were included in the review for comparative purposes only.

Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately $136 million dollars in MHS expenditures in

FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does not accurately represent utilization of the IV agents (e.g., infliximab), since these medications are commonly administered in clinic or office settings and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record. The cost of treatment with these agents is high (on the order of $10,000 to $20,000 annually). There were approximately 11,500 unique TIB utilizers in the MHS in the most recent quarter (June to August 2007), not including patients receiving IV agents.

The majority of use of TIBs in DoD is for the two multi-indication agents (adalimumab and etanercept), not including patients receiving IV agents. Fewer than 4% of DoD TIB utilizers are receiving other TIBs. Over the entire patient population, adalimumab and etanercept are consistently used in about a 2:1 ratio, although utilization in the last quarter (June to August 2007) shows increased uptake of adalimumab among new users (new users only: 44% use of adalimumab vs. 54% use of etanercept, 2% other TIBs).

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept that

a) Across all disease states reviewed, all of the TIBs FDA-indicated for a particular condition have sufficient evidence from placebo-controlled randomized controlled trials (RCTs) to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus methotrexate (MTX) offers better efficacy than TIBs or MTX alone. Beneficial effects on quality of life and productivity are associated with improvements in clinical response.

b) There is a lack of direct comparative evidence (head-to-head RCTs) across all disease states. In all disease states except rheumatoid arthritis (RA), trials were too small in number or too heterogeneous to make indirect comparisons based on meta-analysis of placebo-controlled trials feasible. With two exceptions, treatment effect across agents appeared similar.

c) In RA, anakinra appears to be less efficacious than the TNF inhibitors (adalimumab, etanercept, and infliximab) with respect to effects on symptoms (American College of Rheumatology response), based on indirect comparison of data from placebo-controlled trials.

d) In psoriasis, PASI 75 scores for infliximab appeared consistently higher than with other TIBs used for psoriasis (etanercept, alefacept, and efalizumab), although there is insufficient comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials. An indication for adalimumab for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer support its efficacy for this condition.

e) The multi-indication self-administered TIBs (adalimumab and etanercept) compare favorably to one another. Etanercept did not appear to be efficacious in

Crohn's disease, for which adalimumab is indicated. Adalimumab lacks published evidence in juvenile rheumatoid arthritis (JRA) and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. For disease states in which both are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.

f) Alefacept and efalizumab are FDA-indicated only for psoriasis; they appear to compare favorably to etanercept in terms of treatment effect. Their place in therapy relative to etanercept and infliximab (and potentially adalimumab) in the treatment of psoriasis is probably dependent on factors such as intramuscular administration of alefacept, recommended lab monitoring with both agents, and greater familiarity of providers with the TNF inhibitors.

g) Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported AEs are injection site or infusion reactions (depending on route). Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by Oregon Health & Science University's Drug Effectiveness Review Program reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7). In addition, anakinra is given once daily, as opposed to weekly or every other week dosing for adalimumab and etanercept.

h) The primary safety concerns with TIBs are related to the potential for increased risk of serious adverse events (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious adverse events tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. There is insufficient evidence to draw conclusions about comparative risk of any of these serious adverse events.

   i) There is fair evidence of an increased risk of serious infections (including tuberculosis) for TIBs compared to placebo.

   ii) Observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed.

   iii) Evidence concerning the safety of TIBs in patients with chronic HF and the effects of TIBs on the development of chronic HF is mixed. Data from etanercept and infliximab RCTs evaluating these TIBs for the treatment of chronic HF suggested higher rates of mortality compared to placebo. However, observational studies have reported lower rates of cardiovascular events in RA patients on TNF inhibitors compared to those on conventional therapy.

   iv) All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other

autoimmune disorders have been reported with etanercept, adalimumab, and infliximab.

v) Adalimumab, etanercept, and infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept.

vi) Laboratory monitoring is required or recommended for anakinra (neutrophil counts), alefacept (CD4+ T lymphocyte counts), and efalizumab (platelet counts) due to reports of hematologic abnormalities.

i) There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concomitantly in clinical trials. Based on two combination trials (one with anakinra plus etanercept and one with abatacept plus etanercept), additive effects on the immune system appear to preclude concomitant treatment with more than one TIB.

j) Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), with the exception of a reported higher risk of mortality among chronic HF patients treated with etanercept or infliximab. Potential differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C); the need for dose reduction of anakinra in patients with impaired renal function; and availability of data in pediatric patients (etanercept for JRA; infliximab for pediatric Crohn's disease).

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) For RA, the clinical effectiveness evaluation concluded that anakinra appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for etanercept, adalimumab, and anakinra showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar effectiveness, while anakinra was both more costly and less effective.

b) For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for efalizumab, etanercept, and alefacept showed similar cost effectiveness profiles for all three agents.

c) The UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TIBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 2 opposed, 1 abstained, 1 absent) to recommend that adalimumab, alefacept, and efalizumab be maintained as formulary on the UF and that etanercept and anakinra be classified as non-formulary

under the UF. (See paragraphs 8A, 8B, and 8C on pages 45-59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for etanercept and anakinra. (See paragraph 8D on page 60 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (15 for, 0 opposed, 1abstained, 1 absent): 1) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision.. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8E on pages 60-61 of the P&T Committee minutes.)

Director, TMA, Decision: □ Approved □ Disapproved

Approved, but modified as follows: *Approved as 120 days.*

D. COMMITTEE ACTION: PA REQUIREMENTS AND CRITERIA – Currently, PA criteria apply to four of the five TIBs: adalimumab, anakinra, efalizumab, and etanercept. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that 1) no changes be made to the PA criteria for etanercept, adalimumab, anakinra, and efalizumab, as outlined in Appendix C; 2) that a PA be required for alefacept under the PA criteria outline above; and 3) that the effective date for the alefacept PA be timed to coincide with that established for the UF decision in this class. (See paragraph 8F on page 61 and Appendix C on page 76 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: QLs – Currently, QLs apply to three of the five TIBs. adalimumab, anakinra, and etanercept. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that 1) no changes be made to existing QL/days

supply limits for etanercept, adalimumab, and anakinra. (See paragraph 8G on page 61 and Appendix C on page 74 of the P&T Commit\tee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

F. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that adalimumab be added to the ECF. (See paragraph 8H on page 62 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9) BCF STATUS OF ROSIGLITAZONE

The Pharmacoeconomic Center (PEC) updated the P&T Committee on the latest news/ evidence regarding the safety of the thiazolidinediones (TZD), particularly that of rosiglitazone, the DoD's BCF TZD. The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone and rosiglitazone/metformin from the BCF. Ultimately, the P&T Committee determined that there was sufficient clinical evidence to justify removal of rosiglitazone and rosiglitazone/metformin from the BCF. (See paragraph 9 on page 62 of the P&T Committee minutes).

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to remove rosiglitazone and rosiglitazone/metformin from the BCF.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10) BCF / ECF REVIEW

As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in two current BCF drug classes, analgesics (meloxicam, cyclobenzaprine, and oxycodone/ acetaminophen) and ADHD and narcolepsy agents (methylphenidate IR).

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) the following changes to BCF / ECF listings. (See paragraph 10 on page 62 of the P&T Committee minutes and Appendix D on page 75):

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Analgesics	BCF – Meloxicam (Mobic) oral	Clarify BCF listing to "meloxicam tablets only"	14	0	1	2
	BCF – Cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	Clarify BCF listing to "cyclobenzaprine IR tablets, 5 and 10 mg"	14	0	1	2
	BCF – Oxycodone 5 mg / acetaminophen 325 mg	Clarify BCF listing to "oxycodone 5 mg / acetaminophen 325 mg tablets"	14	0	1	2
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	Clarify BCF listing to "methylphenidate IR (excludes Methylin oral solution and chewable tablets), methylphenidate ER (specific brand name is Concerta); mixed amphetamine salts ER (Adderall XR)"	14	0	1	2

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11) STATUS OF AMLODIPINE ON THE UF

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. At this meeting, the UF status of amlodipine (Norvasc, generics) was re-evaluated due to a significant decrease in cost across all three points of service.

Clinical Effectiveness Conclusion - At the August 2005 P&T Committee meeting, the Committee concluded that, in general, amlodipine had similar clinical effectiveness relative to other DHP CCBs in regards to efficacy, safety, and tolerability.

Cost Effectiveness Conclusion – The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) that amlodipine was the most cost effectiveness DHP CCB.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that amlodipine be reclassified as generic on the UF. (See paragraph 11A on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: UF IMPLEMENTATION PERIOD – The P&T Committee recommend immediate implementation upon signing of the November 2007 DoD P&T Committee minutes by the Director, TMA. (See paragraph 11B on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: BCF REVIEW AND IMPLEMENTATION - The P&T Committee considered the BCF status of the DHP CCB agents. Based on the results of the clinical and economic evaluations presented, the Committee voted (15 for, 0 opposed, 1 abstained and 1 absent) to add amlodipine to the BCF. (See paragraph 11C on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

12) RE-EVALUATION OF NON-FORMULARY AGENTS

The P&T Committee's process for the re-evaluation of non-formulary agents established at the May 2007 meeting was approved by the Director, TMA on 24 June 2007. For this meeting, the PEC applied the appropriate criteria and defined a list of non-formulary drugs for re-evaluation of UF status (Table 3) for the P&T Committee's consideration. Accordingly, the P&T Committee reviewed a list of non-formulary drug agents identified that were: 1) from drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF and not excluded from the UF based on clinical issues alone.

Accordingly, the PEC recommended that the following pre-established criteria be applied to each non-formulary agent for re-evaluation of UF status.

1) The non-formulary agent becomes generically available and:
   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system
   b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.
2) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost effective when:
   a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
   b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

The PEC reminded the DoD P&T Committee that when the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.

1) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.

2) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

COMMITTEE ACTION: The P&T Committee voted (15 for, 1 against, 0 abstained, 1 absent) to recommend that the following list of non-formulary drug agents be re-evaluated for UF status when pre-established criteria are met. (See paragraph 12 on pages 63-65 of the P&T Committee minutes).

Generic Name	Brand Name	UF Class	Generics Shipping?
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
quinapril	Accupril	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan	CCBs	N
verapamil ER HS	Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Implementation Status of UF Recommendations/Decisions
Appendix B – Newly Approved Drugs
Appendix C – Existing Prior Authorization Criteria and Quantity Limits for TIBs
Appendix D - BCF Review
Appendix E – Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

signed 13 Feb 08

S. Ward Casscells, M.D.

Department of Defense
Pharmacy and Therapeutics Committee Minutes
November 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14-15 Nov 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Lt Col Charlene Reith, BSC *for* Col Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Walter Downs, MC *for* LCDR Michelle Perelló, MC	Navy, Internal Medicine Physician
LCDR Ronnie Garcia, MC *for* LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC (P) Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

To be determined	Air Force, Internal Medicine Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Deputy General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plan Operations, TMA

E. Others Present

CDR Matthew Carlberg, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
LTC Chris Conrad, MC, USA	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
Nancy Misel, RPh	Director, Air Force High Dollar Program
LCDR James Ellzy, MC, USN	Prospective DoD P&T Committee Chair
Lt Col Thom Bacon	TMA Pharmaceutical Operations Directorate
CDR Rob Hayes	USPHS/IHS
Melinda Neuhauser	VA PBM

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – August 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of August Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the August 2007 DoD P&T Committee meeting on October 17, 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss, CAPT Blanche and LTC Kelly briefed the members of the P&T Committee regarding the August 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on one new drug which was approved by the FDA (see Appendix B). The P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status; therefore, UF consideration was deferred until the drug class review is completed. The P&T Committee discussed the need for a quantity limit (QL) for formoterol fumarate inhalation solution (Perforomist), based on existing QLs for other oral inhalation products and recommendations for use in product labeling.

COMMITTEE ACTION: QL – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1absent) to recommend a QL for formoterol fumarate inhalation solution of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days**.**

B. Renin Angiotensin Antihypertensive (RAA) – Valsartan/Amlodipine (Exforge)

1) Valsartan/Amlodipine Relative Clinical Effectiveness –The proprietary product Exforge contains the combination of valsartan (Diovan) with amlodipine (Norvasc). It is the first fixed-dose combination product containing an angiotensin receptor blocker (ARB) with a dihydropyridine (DHP) calcium channel blocker (CCB). Generic formulations of amlodipine are now commercially available.

The DoD P&T Committee previously reviewed several subclasses of the RAA drug class, including the angiotensin converting enzyme (ACE) inhibitors and ACE/diuretic combinations in August 2005, the ACE/CCB combinations in February 2006, the ARBs and ARB/diuretic combinations in February 2005 and May 2007, and the direct renin inhibitor aliskiren (Tekturna) in August 2007.

Fixed-dose combination RAA agents designated as UF are benazepril/amlodipine (Lotrel, generics), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT), candesartan/HCTZ (Atacand HCT), losartan/HCTZ (Hyzaar), lisinopril/HCTZ (Prinzide, Zestoretic, generics), captopril/HCTZ (Capozide, generics), benazepril/ HCTZ (Lotensin HCT, generics), enalapril/ HCTZ (Vaseretic, generics), and fosinopril/HCTZ (Monopril HCT, generics).

Valsartan/amlodipine is approved for treating hypertension in patients whose blood pressure (BP) is not adequately controlled with an ARB or DHP CCB administered as monotherapy. Although Exforge is not approved for the initial treatment of hypertension, there is no evidence to suggest that it would not be effective when used in that manner clinically.

With regard to efficacy, combining an ARB with a DHP CCB provides two differing mechanisms to reduce BP. Two randomized controlled trials (RCTs) in over 2,000 patients showed superior BP reduction and control with Exforge compared to valsartan and amlodipine administered as monotherapy, and compared to placebo. A trial in 130 patients with Stage 2 hypertension (>160/>100 mm Hg) found similar BP reductions when valsartan/amlodipine was compared to the fixed dose combination of lisinopril/HCTZ.

There are no clinical trials with valsartan/amlodipine that have evaluated clinical outcomes of reducing mortality, stroke, heart failure (HF) hospitalization, or need for renal dialysis/transplantation. However, valsartan and amlodipine individually have shown benefits in these areas, and there is no evidence to suggest that valsartan/amlodipine would not be beneficial here.

With regard to safety, the package labeling for Exforge reflects that of the individual components for adverse events, drug interactions, and black box warnings (e.g., teratogenicity concerns with ARBs). In clinical trials, the incidence of peripheral edema with valsartan/amlodipine was lower than that observed with amlodipine monotherapy.

Although not specifically evaluated in a controlled clinical trial with valsartan/ amlodipine, potential benefits to fixed dose combination drugs include reduced tablet burden, simplified drug regimens, increased patient convenience, and improved adherence to therapy.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded that, while valsartan/amlodipine offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive agents included on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Valsartan/Amlodipine Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of valsartan/amlodipine in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the ARBs. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

   A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of valsartan/amlodipine. The cost effectiveness of Exforge was evaluated relative to the following pairings of single ingredient agents (ARB plus amlodipine): telmisartan (the most cost effective UF ARB) plus amlodipine; candesartan (chronic HF indication UF ARB) plus amlodipine; valsartan plus amlodipine (single ingredient agents of Exforge).

   The results of the CMA showed that the projected weighted average daily cost of Exforge was significantly higher than the weighted average daily cost of the pairings of UF ARBs with amlodipine.

Cost Effectiveness Conclusion – The P&T Committee concluded that valsartan/ amlodipine is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost effective relative to Exforge.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to accept the valsartan/amlodipine relative cost effectiveness analysis as presented by the PEC.

3) *Valsartan/Amlodipine UF Recommendation*

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of valsartan/amlodipine, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 3 abstained, 2 absent) to recommend that Exforge be designated as non-formulary on the UF.

4) *Valsartan/Amlodipine MN Criteria* - Based on the clinical evaluation of valsartan/amlodipine, and the conditions for establishing medical necessity (MN) for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for Exforge:

   1) Use of the formulary alternatives is contraindicated.
   2) The patient has experienced significant adverse effects from formulary alternatives.
   3) The patient previously responded to the non-formulary agent, and changing to the formulary alternatives would incur unacceptable risk.

   The P&T Committee specifically noted circumstances under which criterion #3 might be considered: 1) post-myocardial infarction (MI) patients with previous angioedema or other intolerance to ACE inhibitors who are stabilized on valsartan/amlodipine and in whom changes in therapy to a formulary ARB plus amlodipine might result in destabilization or 2) chronic HF patients who are stabilized on valsartan/ amlodipine and in whom changes in therapy to a formulary ARB plus amlodipine might result in destabilization.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Valsartan/Amlodipine Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and no later than a 60-day implementation period at military treatment facilities (MTFs). The implementation period will begin immediately following approval by the Director, TMA.

   As part of the implementation plan, the P&T Committee also recommended that the TRICARE Management Activity (TMA) send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for valsartan/amlodipine. A retrospective pharmacy claims analysis revealed that

approximately 2,400 DoD beneficiaries have filled a prescription for valsartan/ amlodipine in the previous quarter.

MTFs will not be allowed to have valsartan/amlodipine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for valsartan/amlodipine written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

C. Attention Deficit Hyperactivity Disorder/Narcolepsy Agent – Lisdexamfetamine dimesylate (Vyvanse)

1) *Lisdexamfetamine Relative Clinical Effectiveness* –Lisdexamfetamine (Vyvanse) is a new stimulant drug approved for treating attention deficit/hyperactivity disorder (ADHD) in children 6 to 12 years of age. In contrast to methylphenidate extended release (ER) (Concerta), mixed amphetamine salts ER (Adderall XR), and atomoxetine (Strattera), lisdexamfetamine is not currently indicated for treating adolescents and adults. Vyvanse and Adderall XR are manufactured by the same company; generic formulations of Adderall XR are anticipated in 2009.

   The ADHD and narcolepsy drugs were evaluated at the November 2006 DoD P&T Committee meeting. The UF designated ADHD drugs include the non-stimulant atomoxetine, and the stimulants dextroamphetamine (Dexedrine, generics), methamphetamine (Desoxyn), mixed amphetamines salts (Adderall, and generics; Adderall XR), and all oral formulations of methylphenidate (Concerta, all Metadate products, all Methylin products, all Ritalin products, and generics). Methylphenidate transdermal system (Daytrana) and dexmethyl-phenidate (Focalin and Focalin XR) were classified as non-formulary.

   With regard to efficacy, there is insufficient evidence to suggest that clinically relevant differences exist between lisdexamfetamine and other ADHD stimulant products. One randomized published trial in 290 children showed significant improvements in ADHD rating scales with lisdexamfetamine compared to placebo. A double-blind, placebo-controlled crossover study available only in abstract form showed significant reductions in observer ratings of ADHD behaviors (e.g., improved ADHD control) with either lisdexamfetamine or mixed amphetamine salts (Adderall XR) in 52 children compared to placebo; outcomes with Vyvanse were not directly compared to Adderall XR.

   With regard to safety, there is no evidence to suggest that the adverse event profile of lisdexamfetamine differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients

report appetite suppression. The package labeling for lisdexamfetamine carries the same black box warning as the other stimulants for tolerance, dependence, abuse potential and sudden cardiac death in children with pre-existing structural cardiovascular abnormalities. The drug interaction profile is the same as other ADHD stimulants, and lisdexamfetamine should not be used concurrently with monoamine oxidase inhibitors, due to the risk of hypertensive crisis.

With regard to abuse potential, lisdexamfetamine is a Schedule II controlled substance, as are the other ADHD stimulants (e.g., methylphenidate and amphetamines). Lisdexamfetamine is a pro-drug that is hydrolyzed in the gastrointestinal tract to dextroamphetamine and the amino acid l-lysine, and was thus designed to have less potential for abuse, diversion and overdose toxicity than amphetamine. Two unpublished studies reported the preference of lisdexamfetamine in a total of 50 drug abusers. At lisdexamfetamine doses less than 100 mg "likeability" scores on a Drug Rating Questionnaire scale were similar to placebo, while doses exceeding 100 mg showed similar likeability as with dextroamphetamine (the maximum recommended lisdexamfetamine dose currently marketed is 70 mg).

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded that lisdexamfetamine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusion stated above.

2) *Lisdexamfetamine Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of lisdexamfetamine in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the other once-daily ADHD stimulant medications. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

   The ADHD stimulants include methylphenidate immediate release (IR) and ER and various immediate and ER formulations of amphetamines (dextroamphetamine, methamphetamine, mixed salts of amphetamine, and lisdexamfetamine). The comparators for the cost effectiveness analysis of lisdexamfetamine included the UF once daily formulations ADHD stimulants: methylphenidate (Concerta, Metadate CD, Ritalin LA), and mixed salts of amphetamine ER (Adderall XR).

   The relative clinical effectiveness evaluation concluded that there is insufficient evidence of a clinically meaningful difference between once daily stimulants for the treatment of ADHD. As a result, a CMA was employed to determine the cost effectiveness of lisdexamfetamine relative to the UF once daily ADHD stimulants.

   Results from the CMA revealed that the weighted average cost per day of therapy for lisdexamfetamine was similar to the other UF once daily ADHD stimulants.

Cost Effectiveness Conclusion – The P&T Committee concluded that lisdexamfetamine had similar relative cost effectiveness compared to the other UF once daily ADHD stimulants.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the lisdexamfetamine relative cost effectiveness analysis as presented by the PEC.

3) *Lisdexamfetamine UF Recommendation*

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of lisdexamfetamine, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstained, 2 absent) to recommend that lisdexamfetamine be designated as non-formulary on the UF. This recommendation was primarily based upon the determination that lisdexamfetamine offers no significant, clinically meaningful therapeutic advantage over other once daily ADHD stimulants.

4) *Lisdexamfetamine MN Criteria* – Based on the clinical evaluation of lisdexamfetamine and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for lisdexamfetamine.

   1) Use of the formulary alternatives is contraindicated.
   2) The patient has experienced significant adverse events from formulary alternatives.
   3) Use of formulary alternatives has resulted in therapeutic failure.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Lisdexamfetamine Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at MTFs no later than a 60-day implementation period.

   As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for lisdexamfetamine. A retrospective pharmacy claims analysis revealed that approximately 2,800 DoD beneficiaries have filled a prescription for lisdexamfetamine in the previous quarter.

   MTFs will not be allowed to have lisdexamfetamine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for lisdexamfetamine written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

   COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday

following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

D. Contraceptive – Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)

1) *Lybrel Relative Clinical Effectiveness* – The contraceptive drug class was reviewed in May 2006. Lybrel is a new contraceptive marketed in July 2007 that contains 20 mcg of ethinyl estradiol (EE) and 90 mcg of levonorgestrel. It is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

   Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel (Lutera, Levlite or equivalent) are included on the Basic Core Formulary (BCF). The Lybrel product cannot be exactly duplicated by using conventional packages of Lutera or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however this difference in the progestin content is of questionable clinical relevance.

   Contraceptives are traditionally available in conventional 28-day packaging containing 21 days of active tablets followed by seven days of placebo tablets, which leads to 13 cycles of withdrawal bleeding yearly. Some recently introduced oral contraceptives reduce the number of placebo tablets to four (Yaz, Loestrin-24 Fe), thus shorting the bleeding period, or extend the number of active tablets to 84, resulting in only four withdrawal bleeding periods per year (e.g., Seasonique, Seasonale). Continuous use of oral contraceptives may be beneficial in women with symptoms related to fluctuations in hormone levels (e.g., endometriosis or menstrual migraines) and in women desiring cessation of cyclical bleeding. Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis. Four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

   With respect to efficacy, there is no evidence to suggest that Lybrel would differ from other similar contraceptives. One head-to-head, open-label trial in 641 women that compared Lybrel with a traditional regimen of 20 mcg EE/100 mg levonorgestrel (Lutera, Levlite or equivalents) reported no difference in pregnancy rates after one year (zero vs. three, respectively). A non-comparative trial in over 2,000 women reported 23 pregnancies after one year (a rate of 1.55 per 100 user years), which is similar to pregnancy rates reported with other contraceptives containing 20 mcg EE.

   With respect to safety, breakthrough bleeding/spotting is common with all extended-cycle or continuous regimens, particularly in the first few months of use. In the non-comparative trial, 18.6% of women discontinued therapy because of uterine bleeding. However, this decreased over time (48% incidence of breakthrough bleeding at pack 3 vs. 21% at pack 13), and approximately 60% of

women achieved amenorrhea after one year. In the head-to-head trial mentioned previously, the incidence of common adverse effects (dysmenorrhea, nausea, and headache) was similar between Lybrel and the comparator (Lutera, Levlite or equivalents). The safety profile of Lybrel has not been evaluated for longer than two years.

Relative Clinical Effectiveness Conclusion: The Committee concluded that Lybrel did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Lybrel Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly other monophasic ethinyl estradiol 20 mcg (M20 EE) contraceptives. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

   The relative clinical effectiveness evaluation concluded that Lybrel does not show compelling clinical superiority over currently available contraceptives on the UF in the M20 EE subclass. As a result, a CMA was employed to determine the cost effectiveness of Lybrel relative to other UF M20 EE agents (Sronyx, Lutera, Levlite-28, Aviane, and Lessina-28) used on a continuous cycle basis.

   The results from the CMA revealed that the weighted average cost per day for treatment for Lybrel is significantly higher than other UF M20 EE agents used on a continuous cycle basis.

   Cost Effectiveness Conclusion. The P&T Committee concluded that Lybrel is not cost effective relative to other UF M20 EE agents used on a continuous cycle basis.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) to accept the ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) relative cost effectiveness analysis as presented by the PEC.

3) *Lybrel UF Recommendation*

   COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the M20 EE contraceptive agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that. Lybrel be designated non-formulary on the UF.

4) *Lybrel MN Criteria* – Based on the clinical evaluation of Lybrel, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for Lybrel:

1) The patient has experienced significant adverse effects from formulary alternatives.

2) Use of formulary alternatives has resulted in therapeutic failure.

The P&T Committee commented that these MN criteria could be expected to apply to Lybrel only rarely, given the wide variety of formulary oral contraceptives—including oral contraceptives containing 20 mcg of EE and 100 mcg of levonorgestrel—all of which can be used on a continuous basis by discarding unneeded placebo tablets. Both criteria would likely only apply to patients who have encountered difficulty with the process of discarding unneeded placebo tablets. The P&T Committee did not expect that the difference between 100 and 90 mcg of levonorgestrel was likely to result in any clinically predictable reduction in adverse effects.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Lybrel Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and no longer than a 60-day implementation period at MTFs. The implementation period will begin immediately following approval by the Director, TMA.

As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for Lybrel. A retrospective pharmacy claims analysis revealed that approximately 273 DoD beneficiaries have filled a prescription for Lybrel in the previous quarter.

MTFs will not be allowed to have ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for Lybrel written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (12 for, 2 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

6. DRUG CLASS REVIEW – ADRENERGIC BETA-BLOCKING AGENTS (ABAs)

The P&T Committee evaluated the relative clinical effectiveness of the 22 adrenergic beta-blocking agents (ABA) marketed in the US (see Table 1). The ABA drug class was subdivided into three categories; ABAs evaluated (but not necessarily FDA-approved) for treating chronic HF; ABAs not evaluated for HF (older ABAs used primarily for hypertension), and ABA/diuretic combinations (one combination product, timolol/HCTZ

(Timozide) has now been discontinued). The current BCF ABAs are metoprolol tartrate (Lopressor, generics) and atenolol (Tenormin, generics).

The ABAs are all available in generic formulations, with the exception of carvedilol extended/controlled release (Coreg CR), which was introduced to the market in March 2007. Generic formulations of carvedilol IR (Coreg) and metoprolol succinate ER (Toprol XL) were launched in mid- to late-2007.

Table 1 ABAs evaluated by the DoD P&T Committee

Generic	Brand	Generic	Brand
ABAs evaluated for chronic heart failure (but not necessarily FDA-approved)		**Older Adrenergic Blocking Agents not evaluated for chronic heart failure; used primarily for hypertension**	
bisoprolol	Zebeta	acebutolol	Sectral
carvedilol	Coreg CR (controlled release) (GlaxoSmithKline)	atenolol	Tenormin
	Coreg (immediate release)	betaxolol	Kerlone
metoprolol tartrate	Lopressor	labetalol	Trandate (Prometheus) Normodyne (Schering; D/C'd)
metoprolol succinate	Toprol XL (Astra Zeneca)	nadolol	Corgard
ABA/ diuretic combinations		penbutolol	Levatol
atenolol / chlorthalidone	Tenoretic	pindolol	Visken
bisoprolol /HCTZ	Ziac	propranolol	Inderal
metoprolol / HCTZ	Lopressor HCT	propranolol extended release	Inderal LA
nadolol / bendroflumethiazide	Corzide	sotalol	Betapace
propranolol / HCTZ	Inderide	sotalol for atrial fibrillation	Betapace AF
timolol / HCTZ	Timozide (discontinued)	timolol	Blockadren

Expenditures for the ABAs exceeded $140 million in FY 07, ranking them in the top 15 drug class expenditures for the Military Health System (MHS). In terms of 30-day equivalent prescriptions dispensed in FY 07, atenolol (Tenormin, generics) is the highest utilized ABA in the MHS (~225,000/month), followed by branded metoprolol succinate (Toprol XL; ~150,000/month), and metoprolol tartrate (Lopressor, generics; ~100,000/ month). Generic formulations of metoprolol succinate (Toprol XL) have exceeded 50,000 30-day equivalent prescriptions since August 2007. Since market introduction, carvedilol ER (Coreg CR) has seen a steady increase in utilization, which exceeded 12,000 30-day equivalent prescriptions dispensed in October 2007.

A. ABAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ABAs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

The P&T Committee focused on the clinical effectiveness of the ABAs for treating cardiovascular disorders, in particular chronic HF; non-cardiovascular uses were not

evaluated. Use of the ABAs for hypertension and acute MI was only briefly discussed, since all of the older ABAs are available in generic formulations and have been commercially available for decades. Additionally other antihypertensive drug classes are now available that are widely used (e.g., ACE inhibitors, ARBs, calcium channel blockers).

1) *Pharmacology* - With respect to pharmacology, the ABAs differ in their selectivity for the beta (β) and alpha (α) receptors. ABAs with β1-selectivity include atenolol (Tenormin, generics), metoprolol succinate (Toprol XL, generics), metoprolol tartrate (Lopressor, generics) and bisoprolol (Zebeta). Cardioselectivity is postulated to reduce adverse pulmonary effects, however selectivity is dose dependent. Carvedilol (Coreg IR and generics; Coreg CR) and labetolol (Trandate, generics) are non-selective ABAs that have equal affinity for β1 and β2 receptor, and also exhibit α-blocking properties, which decreases peripheral vascular resistance via vasodilation.

2) *FDA-Approved Indications* – All of the ABAs and the ABA/diuretic combinations are approved for treating hypertension, with the exception of sotalol (Betapace, Betapace AF, generics). Both metoprolol tartrate and metoprolol succinate are approved for angina. With regards to chronic HF, carvedilol (Coreg, Coreg CR) and metoprolol succinate are indicated for use to reduce the risk of death; however, there are slight differences in the package labeling. Both Coreg IR and Coreg CR are approved for use in patients with mild to severe HF and to reduce the risk of death following MI in patients with left ventricular systolic dysfunction (LVSD). Metoprolol succinate is approved for treating patients with mild to moderately severe HF. Bisoprolol (Zebeta) is not approved for treating HF, but has evidence of a mortality benefit from one clinical trial (see efficacy section).

3) *Labetolol* – Labetolol is similar to carvedilol in that it is a non-selective ABA that also exhibits α receptor blocking properties. However the Committee agreed that clinical comparisons to carvedilol (Coreg, Coreg CR) would not be considered, since labetolol has not been evaluated in the treatment of chronic HF. Niche uses for labetolol include intravenous use for hypertensive urgency/emergency, and use for pregnancy.

4) *Sotalol* – Unlike the other ABAs, sotalol is the only ABA that is not approved for treating hypertension. Two branded formulations are available; Betapace is FDA-approved for treating ventricular arrhythmias, while Betapace AF is specifically labeled for use in maintaining normal sinus rhythm (NSR) in atrial fibrillation and contains instructions for initiating therapy. The Committee did not further evaluate sotalol, as both Betapace and Betapace AF are available in generic formulations.

5) *Carvedilol ER* – The Committee evaluated the pharmacokinetic and pharmacodynamic differences between carvedilol ER and carvedilol IR. Coreg CR is a capsule containing beads with differing release mechanisms. The Committee agreed that with the exception of the time to max concentration (which is delayed with carvedilol extended release), Coreg CR and carvedilol IR show similar kinetic profiles.

6) *Efficacy for hypertension* – The Oregon Health & Science University's Drug Effectiveness Review Program (DERP) first reviewed the beta blockers in 2005, with an update published in 2007. DERP concluded that the ABAs are equally effective at controlling BP in patients with hypertension. No ABA has been shown to be more efficacious than another, either as initial therapy or when added on to a diuretic, ACE inhibitor or ARB.

7) *Efficacy for chronic HF* – The P&T Committee focused on the use of metoprolol succinate, metoprolol tartrate, carvedilol (Coreg, Coreg CR) and bisoprolol for chronic HF. Both formulations of carvedilol are FDA-approved for HF, but the Coreg CR indication was granted solely based on data from carvedilol IR clinical trials.

   a) *Placebo controlled trials* – Placebo controlled trials conducted with bisoprolol (CIBIS-II, metoprolol succinate (MERIT-HF), and carvedilol IR (US Carvedilol Trial) showed reductions in mortality of approximately 30%. Treatment with carvedilol IR showed a 35% reduction in mortality in patients with severe HF (left ventricular ejection fraction <20%) in the COPERNICUS trial. The CAPRICORN trial supported the use of carvedilol IR as it reduced the risk of death by 23% in post-MI patients with LVSD. FDA-approval for carvedilol ER was based on the clinical trial data with carvedilol IR; Coreg CR has not been evaluated in a clinical trial for HF.

   b) *Head-to-head trials* – Clinical outcomes were evaluated with carvedilol IR vs. metoprolol tartrate in the COMET trial, which enrolled over 3,000 patients with mild to moderate HF. After 58 months, treatment with carvedilol resulted in a significant 17% reduction in mortality and a significant 29% reduction in fatal and non-fatal MI. The superiority of carvedilol over metoprolol tartrate seen in this trial has generated controversy, due to concerns of potential non-equivalent dosage comparisons. Metoprolol succinate was not available to the COMET investigators, and has not been evaluated directly with carvedilol.

   c) *National Guidelines* – The 2005 American College of Cardiology/American Heart Association guidelines specifically mention that three ABAs, metoprolol succinate, carvedilol (Coreg, Coreg CR), and bisoprolol, have shown a benefit in reducing mortality in patient with chronic HF. Patients with Stage C HF should receive one of these three ABAs.

8) *Safety and tolerability* - With respect to safety and tolerability, the adverse event profile of the ABAs is well known, and generally recognized as a class effect. In a retrospective study conducted in 268 patients enrolled in a HF clinic, no difference was seen in the percentage of patients started on either carvedilol IR or metoprolol succinate who were switched to the other drug due to tolerability problems with dizziness, fatigue, or dyspnea.

   With respect to safety differences between carvedilol IR and carvedilol ER, conflicting results have been seen. In one comparative trial in patients with hypertension, the overall incidence of adverse events was lower with carvedilol ER than carvedilol IR. However a higher incidence of adverse events with

carvedilol ER was seen at the 80 mg dose vs. 25 mg carvedilol IR in patients with HF.

9) *Other Factors* – Differences in adherence between carvedilol IR and carvedilol ER were evaluated by the P&T Committee. Carvedilol IR requires twice daily (BID) dosing, while carvedilol ER is dosed once daily (QD), which theoretically should improve patient adherence. Systematic reviews conduced with several drug classes other than the ABAs report adherence rates of 79% +/- 14% with QD dosing, vs. 69% +/- 15% with BID dosing. Whether this increase in adherence translates into improved outcomes for the ABAs used for chronic HF remains unclear.

   One manufacturer-sponsored study evaluating differences in compliance rates between carvedilol ER and carvedilol IR found no difference between the two drugs in 269 patients with HF after 5 months of therapy (Coreg CR: 89.3% +/- 20.8 vs. Coreg: 88.1% +/- 24.1%). The clinical applicability of these results is difficult to determine, due to the open-label design of the Coreg CR arm, and the supervised setting of a HF clinic.

10) *Clinical Coverage* – In order to meet the needs of the majority of patients in DoD, the P&T Committee agreed that an ABA with evidence of a mortality benefit in chronic HF must be included on the BCF. The DoD P&T Committee also agreed that an ABA/diuretic combination need not be included on the BCF.

11) *Therapeutic Interchangeability* – With respect to treating hypertension, the ABAs have a high degree of therapeutic interchangeability. With respect to treating chronic HF, there is a high degree of therapeutic interchangeability between carvedilol, metoprolol succinate, and bisoprolol, which have been shown to reduce mortality.

12) *ABA overall clinical effectiveness conclusion* - The DoD P&T Committee concluded that:

   a) Labetolol was not clinically comparable to carvedilol (Coreg; Coreg CR) despite exhibiting alpha blocking properties, as it has not been evaluated for chronic HF.

   b) Sotalol (Betapace, Betapace AF) was not clinically comparable to the other ABAs, as it is not FDA-approved for treating chronic HF.

   c) For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect.

   d) For treating chronic HF, metoprolol succinate, carvedilol (Coreg, Coreg CR), and bisoprolol have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there is no data to suggest that there are differences in the reduction in mortality between carvedilol, metoprolol succinate, or bisoprolol.

   e) Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there

are clinically relevant differences in the adverse event profile between carvedilol IR and carvedilol extended release.

f) Despite the convenience of once daily dosing of carvedilol ER, there is no compelling clinical evidence to suggest a benefit of Coreg CR over carvedilol IR.

g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as non-formulary on the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the conclusions stated above.

B. ABAs – Relative Cost Effectiveness - The P&T Committee evaluated the relative cost effectiveness of the ABAs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

For the economic evaluation, the ABAs were functionally divided into three groups, based on predominant use: 1) ABAs for hypertension, 2) ABAs for chronic HF, and 3) ABAs used for other conditions (e.g., severe hypertension; arrhythmias).

The ABAs for hypertension include acebutolol, atenolol, betaxolol, metoprolol tartrate, nadolol, penbutolol, pindolol, propranolol IR and ER, timolol, and their diuretic combinations of atenolol chlorthalidone, bisoprolol/HCTZ, metoprolol tartrate/HCTZ, nadolol/bendroflumethiazide, propranolol/HCTZ, and timolol/HCTZ (which has now been discontinued).

The ABAs for heart failure include bisoprolol, metoprolol succinate, carvedilol IR, and carvedilol ER.

Lastly, the ABA group for other conditions includes sotalol (Betapace, Betapace AF) for ventricular arrhythmias and maintenance of normal science rhythm in patients with atrial fibrillation/flutter and labetolol for hypertension and severe hypertension.

The relative clinical effectiveness evaluation concluded that: 1) for hypertension, ABAs are highly clinically interchangeable when titrated to effect, and 2) for chronic HF, there is insufficient evidence to suggest clinically significant differences between agents [e.g. metoprolol succinate vs. carvedilol (Coreg, Coreg CR) vs. bisoprolol] or between different dosage forms approved for chronic HF (e.g. carvedilol IR vs. carvedilol CR). As a result, CMAs were conducted for each subgroup to compare the relative cost effectiveness of these agents.

Results from the cost effectiveness analyses revealed:

For hypertension,

1) The three most cost effective agents are atenolol, metoprolol tartrate, and propranolol IR, which account for 90% of the hypertensive ABA utilization.

2) The other agents are more costly and have lower utilization relative to the top three, but all of these agents are generically available and are considered to be cost-effective.

For heart failure,

1) Carvedilol IR is the most cost effective ABA followed closely by (ranked from most to least cost effective) bisoprolol, metoprolol succinate, and carvedilol ER.
2) The system-wide weighted average cost per day for carvedilol ER was only slightly higher than that of carvedilol IR, and thus was determined to be cost effective relative to the other ABAs for chronic HF.

For other conditions,

1) Sotalol, sotalol AF, and labetalol are all available in generic formulations and are cost-effective.

A budget impact analysis (BIA) was performed to examine the potential budget impact of a UF scenario with carvedilol ER designated as formulary on the UF versus a one with carvedilol ER designated as non-formulary under the UF. The BIA showed that the scenario that designated carvedilol ER as formulary on the UF resulted in significantly lower MHS expenditures versus the scenario that designated carvedilol ER as non-formulary under the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded for consideration of UF status that:

1) All ABAs used primarily to treat hypertension are cost-effective, with atenolol, metoprolol tartrate, and propranolol IR being the most cost-effective.
2) All of the ABAs with clinical evidence for heart failure are cost-effective, with carvedilol IR being the most effective agent.
3) The ABAs for other indications, sotalol, sotalol AF, and labetalol are cost-effective.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the cost effectiveness conclusion stated above.

C. ABAs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that. atenolol, atenolol-chlorthalidone, metoprolol tartrate, metoprolol succinate, propranolol, propranolol/HCTZ, propranolol ER, timolol, timolol/HCTZ, bisoprolol, bisoprolol/HCTZ, nadolol, nadolol/bendroflumethiazide, acebutolol, betaxolol, penbutolol, carvedilol IR, and carvedilol ER be designated formulary on the UF.

D. ABAs – BCF Review and Recommendations

COMMITTEE ACTION– The P&T Committee considered the BCF status of the ABA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to

recommend that atenolol and metoprolol tartrate be maintained and to add generic formulations of carvedilol IR and metoprolol succinate to the BCF.

7. DRUG CLASS REVIEW – ALPHA BLOCKERS (ABs) FOR BENIGN PROSTATIC HYPERTROPHY (BPH)

A. BPH Alpha Blockers – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ABs used for BPH that are currently marketed in the US. The BPH ABs comprises the non-uroselective agents terazosin (Hytrin, generics) and (Cardura, Cardura XL, generics), and the uroselective agents alfuzosin (Uroxatral) and tamsulosin (Flomax). The BPH AB class was first reviewed by the DoD P&T Committee in August 2005. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) *FDA-approved indications* – Terazosin, doxazosin, alfuzosin, and tamsulosin are FDA-approved for treating the signs and symptoms of BPH.

2) *Efficacy measures* - The primary outcome measures used to assess BPH AB efficacy are changes in symptom scores [e.g., American Urological Association Symptom Index (AUA-SI) or international prostate symptom score (IPSS)], and urinary flow rate (Qmax). In clinical trials, a decrease in symptom score of three or more points is generally considered clinically significant, although men self-rate decreases of one to two points as slightly improved symptoms. A change in urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) *Efficacy*

   a) *Meta-analyses/systematic reviews* – A meta-analysis [AUA 2003], systematic reviews [Djavan 1999, Clifford & Farmer 2000, Wilt 2002,2003], and pooled analysis concluded that the ABs were effective, and consistently improved lower urinary tract symptoms (LUTS) and Qmax compared to placebo. The ABs produced comparable improvements in LUTS and Qmax.

   b) *Placebo-controlled studies* - Placebo-controlled studies have demonstrated improvements in total symptom score from baseline of about 30% to 50% for the ABs vs. about 10% to 30% for placebo. On average, terazosin reduced AUA-SI score by 3 points; tamsulosin by 3 points [Wilt 2002, 2003]; doxazosin by 3 points at 1 year [Kirby 2003] and 2 points at 4 years, [McConnell 2003]; and alfuzosin by 2 points short-term [MacDonald 2005], more than placebo. Improvements in Qmax for the ABs were about 5% to 15% greater than placebo [Djavan 1999, Clifford & Farmer 2000, Wilt 2002, 2003, Roehrborn 2001].

A rapid response (within 2 weeks) was seen with most ABs. Improvement with tamsulosin has been observed after the first dose, with peak effects occurring after one week [Djavan 1999, 2004]. Alfuzosin has also demonstrated improvement after the first-dose [Djavan 1999, Roehrborn 2001].

c) *Head-to-head trials* - Head-to-head trials and indirect comparative studies (e.g., meta-analysis and systematic reviews) between ABs when used at equivalent doses do not show clinically relevant difference in efficacy, in terms of symptom relief and urodynamic improvements. Overall, for the ABs, total symptom score improved by 30% to 40% relative to baseline and Qmax by 16% to 29%.

d) *Newly published clinical trials* - Since the prior August 2005 DoD P&T Committee review, only two randomized controlled trials and three quality of life (QoL) studies were identified.

- *Nordling 2005* – The first trial was a double-blind, placebo-controlled trial that indirectly compared alfuzosin10 mg or 15 mg or tamsulosin 0.4 mg to placebo. Although alfuzosin and tamsulosin were not directly compared to each other, significant symptoms improvement occurred when both treatments were administered at the recommended doses (i.e., alfuzosin 10 mg, tamsulosin 0.4 mg) compared to placebo. The IPSS change from baseline was similar with both agents.
- *Roehrborn 2006* - The second double-blinded, placebo-controlled study demonstrated that alfuzosin prevented/slowed the overall clinical progression of BPH after 2 years, but did not reduce the risk of acute urinary retention or need for surgery. Alfuzosin reduced AUA-SI score by 1 point, and improved QoL compared to placebo.
- *Elhilali 2006, Flannery 2006, Hartung 2006* - Three non controlled open-labeled studies conducted in the primary care setting suggested that both alfuzosin and tamsulosin improved QoL measures in addition to improving LUTS.
- *Conclusion for new information since 2005* - No newly published U.S. head-to-head trials were identified since the 2005 review was conducted. Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH.

e) *Efficacy conclusion*- Based on limited head-to-head trials and indirect comparisons between the agents the following conclusions can be made:

- The existing evidence does not support clinically significant differences in efficacy between terazosin, doxazosin, tamsulosin, and alfuzosin.
- All the ABs produce clinically significant symptom improvements when compared to placebo. Results of the AUA meta-analysis suggest terazosin, doxazosin, alfuzosin, and tamsulosin are similar in efficacy, based on partial relief of symptoms and improvement in the AUA-SI Score. Other systematic reviews, meta-analyses, and clinical trials agree with the AUA meta-analysis.

- There are no published head-to-head trials directly comparing alfuzosin with tamsulosin. One trial published since 2005 [Nordling] that indirectly compared alfuzosin or tamsulosin with placebo reported significant symptom improvement with both treatments. Existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

4) *Safety / Tolerability*

a) *Adverse reactions* – The most commonly reported adverse events with the ABs during placebo controlled and open label uncontrolled studies are vasodilatory in nature (e.g., dizziness, asthenia/fatigue, headache, and hypotension). The incidence of vasodilatory effects with alfuzosin and tamsulosin are relatively low. Postural hypotension occurred in approximately 3% of patients treated with tamsulosin and in less than 1% of patients treated with alfuzosin. Asthenia and dizziness were reported in a higher percentage of tamsulosin (7-8%) and alfuzosin (3-4%) treated patients compared to placebo. Adverse events associated with ABs are dose dependent, with a higher incidence reported with higher doses compared to low dose or placebo.

b) *Discontinuation rates* – Discontinuation rates due to adverse events range between 4% to 10% for tamsulosin and alfuzosin, which is comparable to placebo. For terazosin and doxazosin, the percentage of patients who discontinued treatment due to adverse events was 8% to 20%.

c) *Syncope and orthostatic hypotension* **–** The package labeling for all four ABs contain a warning for syncope and orthostatic hypotension; however, these events are more prevalent with terazosin and doxazosin. As a result, terazosin and doxazosin require dose titration when treatment is initiated. In clinical trials, tamsulosin and alfuzosin either do not decrease BP to a clinically significant extent, or reduce BP similar to placebo. Tamsulosin and alfuzosin may be better options for patients with BPH who cannot tolerate a BP reductions, or orthostatic changes in BP, heart rate, or peripheral vascular responsiveness.

d) *Sexual Dysfunction* – The package labeling for tamsulosin carries a warning concerning the risk of priapism. Although alfuzosin labeling does not contain a warning for priapism, post-marketing cases have been reported. Data from the AUA meta-analysis estimated that the rate of ejaculatory dysfunction with tamsulosin was 10%. The incidence of ejaculatory dysfunction with alfuzosin, terazosin, and doxazosin were approximately 1% in placebo-controlled trials.

e) *Drug-drug interactions* – Drug interactions are more of an issue with alfuzosin and tamsulosin compared to doxazosin and terazosin. Alfuzosin is contra-indicated for concomitant use with potent cytochrome P450 (CYP) 3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Tamsulosin has potential drugs interactions with cimetidine and warfarin.

f) *Drug-drug interactions with phosphodiesterase Type 5 (PDE-5) inhibitors* – PDE-5 inhibitors (sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)]

are mild vasodilators, which may decrease BP. Concomitant use of PDE-5 inhibitors with any AB may evoke orthostatic hypotension.

g) *Special populations* – Terazosin and doxazosin are rated pregnancy category C, while alfuzosin and tamsulosin are rated pregnancy category B. No AB is indicated for use in women. Doxazosin should be used with caution in patients with hepatic failure. Alfuzosin is contraindicated in patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), and caution is recommended in patients with severe renal insufficiency. Alfuzosin should be used with caution in patients with a history of QT prolongation or who are receiving concomitant medications with the potential for QT prolongation. The effect of terazosin, doxazosin, and tamsulosin on the QT interval has not been studied. Allergic reactions with tamsulosin have been reported in patients with sulfa allergy.

h) *Dose titration* – Each time there is a period of noncompliance with terazosin or doxazosin, dosage titration from the lowest dose will be necessary to avoid potential problems with orthostatic hypotension. Dosage titration after non-compliance episodes is not necessary with alfuzosin or terazosin.

i) *Intraoperative Floppy Iris Syndrome (IFIS)* –Tamsulosin can cause a potential intraoperative complication, IFIS, during cataract surgery. IFIS was a recently described phenomenon affecting cataract surgery at the time of the 2005 review. To date, several case reports and observational studies have connected IFIS with tamsulosin use [Blouin 2007, Chang 2005, Chadha 2007, Cheung 2007, Parssinen 2006, Oshika 2007, Takmaz 2007]. The literature has a few anecdotal case reports of IFIS occurring with alfuzosin [Blouin 2007, Settas 2006], terazosin, and doxazosin [Chadha 2007, Parmar 2005]. Data from the FDA) Adverse Event Reporting System (AERS) identified isolated cases suggestive of IFIS with tamsulosin, doxazosin, terazosin, and the 5-alpha reductase inhibitor finasteride (Proscar), and has included this as a precaution in all AB package labeling.

j) *Safety and tolerability conclusion*- Vasodilatory adverse events were reported most commonly with the ABs during placebo-controlled and open label uncontrolled trials. Dizziness and asthenia most commonly lead to discontinuation of therapy. Alfuzosin and tamsulosin appear well-tolerated; there are only a few differences in safety considerations (e.g., drug interactions with CYP3A4 inhibitors; precautions for QT prolongation). Data from the clinical trials published since 2005 did not add substantial new information as to safety, tolerability or adverse events.

5) *Other Factors*

Provider Input: Results from a survey sent to MTF providers indicated that alfuzosin and tamsulosin had similar effectiveness, safety and tolerability profiles.

6) *Therapeutically Interchangeability*

Terazosin and doxazosin the non-uroselective ABs, have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin, the uroselective AB, in terms of

safety/tolerability. The non-uroselective agents have a high incidence of discontinuation rates and vasodilatory effects than the non-uroselective agents.

For the uroselective ABs alfuzosin and tamsulosin, there is a high degree of therapeutic interchangeability with regards to efficacy, safety, and tolerability.

7) Clinical Coverage

Neither alfuzosin nor tamsulosin offers a unique benefit over the other. It is not likely that a patient who did not have an adequate response with one uroselective AB would have a better response with the other. Either alfuzosin or tamsulosin could be expected to meet the needs of the majority of the DoD patients requiring a uroselective agent.

There is no evidence to suggest switching between the four ABs would provide additional benefit to patients who fail treatment due to lack of effectiveness. Patients with an inadequate response to the ABs would be candidates for a 5-alpha reductase inhibitor or surgery. To meet the needs of the majority of the patients in DoD, one non-uroselective AB and one uroselective AB (for patients who can not tolerate a non-uroselective AB) is required.

8) Clinical Effectiveness Conclusion - The P&T Committee concluded that:

a) Based on randomized placebo-controlled trials, terazosin, doxazosin, tamsulosin, and alfuzosin were found to produce clinically significant and comparable symptom improvements when compared to placebo.

b) Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

c) There appear to be few differences in the incidence of adverse effects with alfuzosin and tamsulosin, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are vasodilatory effects.

d) There appear to be major differences in withdrawal rates due to adverse events between non-uroselective (terazosin and doxazosin) and the uroselective agents (alfuzosin and tamsulosin). Withdrawal rates reported in clinical trials were low overall for alfuzosin and tamsulosin.

e) The package labeling for alfuzosin contains cautions for QT prolongation effects. The effect of tamsulosin on the QT interval has not been studied.

f) Alfuzosin is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Tamsulosin has potential drug interactions with cimetidine and warfarin.

g) Doxazosin should be used with caution in men with hepatic failure. Alfuzosin is contraindicated in men with moderate to severe hepatic impairment (Child-Pugh categories B and C). Tamsulosin does not require dosage adjustment in men with moderate hepatic dysfunction.

h) Package labeling for all four ABs contains information regarding the potential for IFIS. For patients receiving alfuzosin and tamsulosin consultation with an ophthalmologist is recommended prior to cataract surgery.

i) Terazosin and doxazosin have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin in terms of safety/tolerability due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective ABs.

j) Alfuzosin and tamsulosin have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of DoD BPH patients requiring an uroselective agent.

k) Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH, or for safety profiles between the uroselective ABs.

l) Based on clinical issues alone, there are no compelling reasons to classify any of the AB agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. BPH Alpha Blockers – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the BPH ABs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e) (2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the uroselective AB medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, a CMA was performed to compare the relative cost effectiveness of potential UF uroselective ABs scenarios. The CMA compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service. The potential UF uroselective ABs scenarios considered were derived from the following condition sets:

1) One selective BPH-AB will be selected to the UF and the BCF. In addition, a PA process would require all new selective BPH-AB users to complete an adequate trial of the UF selective BPH-AB before the non-formulary selective BPH-AB is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy. (1 UF, 1 BCF, with PA)

2) One selective BPH-AB will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (1 UF, 0-1 BCF).

3) Two or more selective BPH-ABs will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (2+ UF, 0-1 BCF)

Results from the AB CMA showed that: 1) UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step

Therapy to be the most cost effective UF scenario considered; 2) UF scenario, under condition set #2, with alfuzosin as the one uroselective agent on the UF and BCF without Step Therapy was the next most cost effective UF scenario considered. However, under this UF scenario, without Step Therapy, the weighted average cost per day of therapy increased by 53% over the most cost effective UF scenario; 3) any condition set that included tamsulosin on the UF was more costly compared to the baseline (what DoD pays today) weighted average cost per day of therapy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which uroselective AB best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS. The results of the BIA paralleled those of the cost effectiveness analysis. The UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step Therapy was the most cost effective UF scenario.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that maintained alfuzosin as the only uroselective agent on the UF and BCF in conjunction with a step therapy/PA was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the AB relative CEA as presented by the PEC.

C. BPH Alpha Blockers – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) alfuzosin be maintained as the uroselective formulary AB, and that terazosin and doxazosin be maintained as the non-uroselective formulary ABs; and 2) tamsulosin be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin for new patients.

D. BPH Alpha Blockers – PA Criteria

The P&T Committee agreed that the following PA criteria should apply to tamsulosin. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

    c) The patient has received a prescription for either tamsulosin or alfuzosin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

    d) The patient has tried alfuzosin and had an inadequate response or was unable to tolerate treatment due to adverse effects.

e) Treatment with alfuzosin is contraindicated.

The P&T Committee noted that in order for a patient to receive tamsulosin at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for tamsulosin would NOT automatically receive it at the formulary cost-share.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend the PA criteria outlined above.

E. BPH Alpha Blockers – MN Criteria

Based on the clinical evaluation for tamsulosin and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for tamsulosin:

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the MN criteria outlined above.

F. BPH Alpha Blockers – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in TMOP program and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tamsulosin on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for non-formulary AB agent written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 1 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. BPH Alpha Blockers – BCF Review and Recommendation

COMMITTEE ACTION: The P&T Committee considered the BCF status of the AB agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry terazosin and alfuzosin.

8. DRUG CLASS REVIEW – TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs)

A. TIBs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the TIBs currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The TIB class is comprised of five medications covered as part of the DoD pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). Three similar biologic agents are not part of the pharmacy benefit due to their intravenous (IV) route of administration: abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). Like adalimumab and etanercept, infliximab is approved for multiple indications and in many respects directly competes with these two self-administered multiple indication agents. The IV agents were included in the review for comparative purposes only. (See Table 2.)

Table 2. FDA-Approved Indications for Targeted Immunomodulatory Biologics (TIBs)

Brand	Generic	Manufacturer	How Given	RA	JRA	PsA	AS	Plaque psoriasis	Crohn's Disease	UC
Enbrel	etanercept	Amgen/Wyeth	SQ	X	X	X	X	X		
Humira	adalimumab	Abbott	SQ	X	*	X	X	*	X	
Kineret	anakinra	Amgen	SQ	X						
Raptiva	efalizumab	Genentech	SQ					X		
Amevive	alefacept	Astellas	IM/IV					X		
Not part of outpatient pharmacy benefit										
Remicade	infliximab	Centocor	IV	X		X		X	X	X
Orencia	abatacept	BMS	IV	X						
Rituxan**	rituximab	Genentech	IV	X						

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL =; SQ = subcutaneous; IM = intramuscular; IV = intravenous
* The Food and Drug Administration is currently considering adalimumab (Humira) for the treatment of JRA and plaque psoriasis.
** Rituxan is also approved for non-Hodgkin's lymphoma.

Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately $136 million dollars in MHS expenditures in FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does not accurately represent utilization of the IV agents (e.g., infliximab), since these medications are commonly administered in clinic or office settings and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record. The cost of treatment with these agents is high (on the order of $10,000 to $20,000 annually). There were

approximately 11,500 unique TIB utilizers in the MHS in the most recent quarter (June to August 2007), not including patients receiving IV agents.

The majority of use of TIBs in DoD is for the two multi-indication agents (adalimumab and etanercept), not including patients receiving IV agents. Fewer than 4% of DoD TIB utilizers are receiving other TIBs. Over the entire patient population, adalimumab and etanercept are consistently used in about a 2:1 ratio, although utilization in the last quarter (June to August 2007) shows increased uptake of adalimumab among new users (new users only: 44% use of adalimumab vs. 54% use of etanercept, 2% other TIBs).

1) Pharmacology and Clinical Use

TIBs are used to treat a variety of serious disease states. Based on an analysis of TIB prescriptions for patients with relevant diagnosis codes in the MHS Mart (M2) over a six-month period (January through June 2007), the most commonly treated condition treated with TIBs in DoD is rheumatoid arthritis (RA). About 73% of TIB patients are being treated for RA. Other conditions include psoriasis (15%), psoriatic arthritis (PsA) (7%), ankylosing spondylitis (AS) (4%), as well as Crohn's disease, juvenile rheumatoid arthritis (JRA), and ulcerative colitis (UC) (all less than 1% each). In most cases the TIBs are indicated as treatment for moderate to severe cases of these conditions, usually following an inadequate response to initial therapy.

Table 3. Dosing and Administration of the TIBs

Brand	Generic	Dosing
Enbrel	etanercept	**RA, PsA, AS** – 25 mg twice weekly or 50 mg once weekly SQ **JRA** (4-17 years) – 0.8 mg/kg per week (maximum 50 mg per week), given once or twice per week SQ **Plaque psoriasis** – 50 mg twice weekly SQ for 3 months, then decrease to 50 mg SQ weekly
Humira	adalimumab	**RA** – 40 mg every other week SQ, may increase to 40 mg q week for monotherapy **PsA, AS** – 40 mg every other week SQ **Crohn's** – 160 mg at week 0, 80 mg at week 2, then 40 mg every other week beginning week 4
Kineret	anakinra	**RA** – 100 mg daily SQ (consider 100 mg every other day SQ in patients with severe renal insufficiency or end stage renal disease)
Raptiva	efalizumab	**Plaque psoriasis** – Initial 0.7 mg/kg SQ injection, then 1 mg/kg weekly SQ injections (not to exceed 200 mg)
Amevive	alefacept	**Plaque psoriasis** – 15 mg once weekly IM; continue for 12 weeks; after a 12-week interval, may retreat with an additional 12-week course if CD4+ T lymphocyte counts are >250 cells/μL
Not part of outpatient pharmacy benefit		
Remicade	infliximab	**RA (adult)** – 3 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to maximum of 10 mg/kg every 4 weeks) **RA (pediatric; 6-17 years)** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks **Crohn's** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to 10 mg/kg) **PsA -** 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks **AS** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 6 weeks **UC, plaque psoriasis** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks Doses > 5 mg/kg per day are contraindicated in patients with moderate to severe heart failure.
Orencia	abatacept	**RA** – IV based on body weight <60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); initial dose at 0, 2, 4 weeks, then every 4 weeks
Rituxan	rituximab	**RA** – 1000 mg IV infusion on days 1 and 15 in combination with methotrexate. Safety and efficacy of retreatment not established.

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL =; SQ = subcutaneous; IM = intramuscular; IV = intravenous

The TIBs target various mediators of the inflammation cascade, effectively retarding the extent and severity of inflammation at the local level. Etanercept,

adalimumab, and infliximab all act through inhibition of tumor necrosis factor-alpha (TNF-α). Adalimumab and infliximab are monoclonal antibodies; they bind specifically to TNF-α, blocking interaction with the p55 and p75 cell surface TNF receptors. Etanercept is a soluble receptor to TNF- α that binds circulating TNF-α and lymphotoxin-α, preventing interaction with cell surface receptors. Anakinra (which is FDA-indicated only for RA) is a human recombinant protein that competitively blocks the interleukin (IL)-1 receptor, blocking inflammatory and immunological responses.

The other TIBs affect T cell (alefacept, efalizumab, abatacept) or B cell (rituximab) involvement in autoimmune and inflammatory processes. Alefacept and efalizumab are FDA-indicated only for the treatment of plaque psoriasis, while the IV agents abatacept and rituximab are FDA-indicated only for RA.

Dosing of the various agents varies from every 8 weeks via IV infusion (infliximab) to daily subcutaneous dosing (anakinra) (See Table 3).

The two multi-indication self-administered TIBs, adalimumab and etanercept, are given every 1 or 2 weeks (see Table 2). Major areas of uncertainty about actual dosing of the TIBs (which may affect safety, tolerability, and efficacy as well as cost) are: 1) the percent of RA patients who receive weekly rather than every other week dosing with adalimumab; 2) the percent of plaque psoriasis patients who continue to receive twice weekly dosing with etanercept 50 mg following the 12-week induction phase; and 3) the percent of patients who receive higher or more frequent doses of infliximab for the treatment of RA and Crohn's disease.

2) Efficacy

A recent well-done systematic review of the drugs in this class is available from the Oregon Health & Science University's DERP. The January 2007 review included published clinical trials through August 2006. The review took a "best evidence" approach, with a primary focus on health outcomes (symptoms, QoL, functional capacity, hospitalizations, and mortality). Radiological changes were considered as a secondary, intermediate measure.

Many TIB trials, particularly in rheumatologic conditions, included treatment with disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), either as monotherapy or in combination with a TIB. (Although the term DMARD technically includes the TIBs, which slow disease progression in RA, it is used in this evaluation to refer solely to non-biologic agents that slow disease progression in RA, such as MTX, sulfasalazine, gold salts, and hydroxylchloroquine.) Since there are no head-to-head RCTs comparing two or more TIBs, comparisons between TIBs in any given disease state primarily rest on the results of placebo- and/or active-controlled RCTs.

As part of its evaluation of the TIB class, the P&T Committee considered summary efficacy and safety data and conclusions from the DERP review, along with more recently published clinical data following the same general approach. Unpublished data provided by pharmaceutical manufacturers as part of their Academy of Managed Care Pharmacy "dossiers" were also considered when little

published data were available (published trials have undergone peer review and are generally considered more reliable than unpublished data). Additional information (typically from open label extension trials or observational studies) was also considered to address questions concerning switching between the TIBs (e.g., in patients refractory to treatment), long-term efficacy and safety, and effects on QoL and productivity.

Few published guidelines to date attempt to establish the place of specific TIBs in the treatment of the disease states addressed in this evaluation.

a) Rheumatoid Arthritis

A prominent RA efficacy measure is the number of patients attaining a American College of Rheumatology (ACR) 20, 50 , or 70 response, based on at least a 20, 50, or 70% reduction compared to baseline in tender / swollen joint counts plus improvements in at least three other specified measures of pain, overall effect, or laboratory measures of inflammation. DERP reviewers chose an ACR 50 response as the outcome measure for adjusted indirect comparisons of randomized placebo controlled trials because it was felt to translate to a clinically significant improvement in health-related QoL.

Based both on trials included in the DERP review and more recently published trials, there is good-to-fair evidence from meta-analyses and large placebo-controlled RCTs supporting the efficacy of etanercept, adalimumab, and anakinra for the treatment of RA. The same is true for the IV agents infliximab, abatacept, and rituximab. Alefacept and efalizumab lack evidence for the treatment of RA. In general, combination treatment with TIBs plus MTX offered better efficacy than TIBs or MTX alone. The same was true of the DMARD sulfasalazine based on one trial. Beneficial effects on QoL and productivity were associated with improvements in clinical response.

Meta-analysis results from the DERP review suggested no significant difference in efficacy among etanercept, adalimumab, and infliximab for the treatment of RA. Point estimates favored the TNF inhibitors (etanercept, adalimumab, and infliximab) over the IL-1 inhibitor anakinra, although differences were statistically significant only for ACR 20 and not ACR 50 response. A recent high-quality meta-analysis [Nixon et al, 2007] similarly reported comparable efficacy among etanercept, adalimumab, and infliximab for the treatment of RA. An analysis comparing anakinra to the TNF inhibitors as a class concluded that the TNF inhibitors were statistically significantly more efficacious than anakinra (OR 1.96, 95% CI 1.03 to 4.01 for ACR 20; OR 1.93, 95% CI of 1.05 to 3.50 for ACR 50).

Numerous studies have shown clinical benefit in patients switching from one TIB to another, including patients switching from infliximab to etanercept, etanercept to infliximab, etanercept to adalimumab, infliximab to adalimumab, and TNF inhibitors to rituximab or abatacept. In general, clinical response was seen with the second TIB regardless of the reason for switching—albeit at lower rates than in TIB-naïve patients—with no increase in adverse events. This appeared to be true both for switches between TNF

inhibitors and from a TNF inhibitor to another TIB. Data on the efficacy of switching to a third TNF inhibitor are mixed.

Another important aspect of overall efficacy concerns the impact of TIBs and other DMARDs on delaying the progressive structural destruction of peripheral joints seen in RA. A common measure is the Total Sharp Score (TSS), which is based on evaluation of x-rays of hands and feet scored for joint erosions and joint space narrowing. Optimally, treatment would both control RA symptoms and delay (or even halt) radiographic disease progression.

Long-term data supporting maintenance of effects on clinical measures (e.g., ACR response) is available for all the TIBs used for the treatment of RA; however, the length of follow-up varies. The longest-term data are available for adalimumab and etanercept (4 to 7 years). Both of these TIBs have evidence supporting delay in radiographic progression for up to 2 years. Infliximab and abatacept have 1-year data supporting sustained effects on clinical measures and radiographic progression. Anakinra has data supporting sustained effects on clinical measures for up to 1 year, but radiographic data only out to 6 months; rituximab lacks radiographic data but has data supporting sustained effect on clinical measures for up to 2 years (following one course of therapy).

b) Juvenile Rheumatoid Arthritis

Etanercept is the only TIB with published evidence that demonstrates efficacy for the treatment of JRA and the only TIB indicated for this condition. Evidence is limited to a single placebo-controlled RCT; similar results are reported in a retrospective analysis of registry data from Germany in pediatric patients with various forms of arthritis. A small, uncontrolled open-label study provides insufficient evidence for infliximab.

Unpublished evidence suggesting efficacy for adalimumab in JRA is available from the manufacturer; FDA approval of adalimumab for this indication is pending.

There is some uncontrolled or observational evidence with infliximab, etanercept, and adalimumab for the treatment of JRA-associated uveitis.

c) Ankylosing Spondylitis

AS causes inflammation of the spine and large joints, resulting in stiffness and pain and often progressive disability. Clinical measures are based on improvement in symptoms such as pain, morning stiffness, fatigue, and mobility. Non-biologic DMARDs are not consistently helpful for the treatment of AS.

Based both on trials included in the DERP review and more recently published trials, sufficient evidence exists to support efficacy of adalimumab, etanercept, and infliximab for treatment of AS symptoms over a period of one to three years, compared to placebo. It is not known if long-term treatment with TNF inhibitors or other biologics can alter the progression of AS. There

is insufficient evidence to conclude that there are differences in comparative efficacy.

One trial provided evidence of successful switching from infliximab to etanercept in patients with loss of efficacy or adverse events on infliximab. There are insufficient data to generalize these results across all treatments.

d) Psoriatic Arthritis

PsA is a chronic inflammatory arthritis associated with psoriasis. Approximately 10 to 30% of psoriasis patients will develop PsA; the psoriasis usually predates the arthritis by many years. Many RA measures are also used in PsA.

Based both on trials included in the DERP review and more recently published trials, evidence from seven placebo-controlled trials supports efficacy of etanercept (two trials), infliximab (two trials), and adalimumab (three trials) in the treatment of PsA. There is insufficient evidence to conclude that there are differences in comparative efficacy among these three agents. A high-quality meta-analysis of placebo-controlled trials [Woolacott et al, 2007] showed very similar treatment effects between etanercept and infliximab.

Long-term data out to 2 years is available for all three agents, including evidence supporting sustained effects on clinical measures of response and radiographic progression.

One trial with efalizumab (which is FDA indicated only for the treatment of plaque psoriasis) reported negative results in PsA. No statistically significant difference in ACR 20 response was seen at 12 weeks, compared to placebo.

e) Plaque Psoriasis

In psoriasis, an environmental trigger is thought to evoke an inflammatory response and subsequent hyperproliferation of keratinocytes, associated with activation of T cells which migrate from the vasculature into the dermal tissues.

A prominent clinical measure of disease severity is the Psoriasis Area and Severity Index (PASI), which incorporates measures of scaling, erythema, and induration of the head, trunk, upper and lower limbs, weighted by severity and affected body surface area. PASI 50/75/90/100 scores represent improvements from baseline in PASI score and are typically reported as the percentages of patients achieving a certain PASI improvement. A PASI 75 response is considered to be the benchmark for current therapies, particularly the biologics.

Based both on trials included in the DERP review and more recently published trials, evidence from published placebo-controlled RCTs supports efficacy of adalimumab (one trial), alefacept (two trials), efalizumab (four trials), etanercept (four trials), and infliximab (three trials) in the treatment of plaque psoriasis.

Due to lack of direct comparative data, it is difficult to draw conclusions regarding comparative efficacy. However, PASI 75 response rates appear consistently higher for infliximab compared to the other TIBs used for the treatment of plaque psoriasis, although some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials.

Evidence for adalimumab in psoriasis includes one published RCT [Gordon et al, 2006] and additional unpublished data available from the manufacturer. FDA approval of adalimumab for plaque psoriasis is pending.

f) Crohn's Disease

Crohn's disease is a chronic inflammatory disease primarily involving the small and large intestine. In its most severe form, it can be associated with the development of deep ulcers and fistulas that can penetrate into adjoining structures or even to the surface skin, leading to infection. The spread of inflammation and thickening of the bowel wall can lead to bowel obstruction. Symptoms may include diarrhea, abdominal pain, anemia, and weight loss. Treatments include 5-aminosalicylic acid, antibiotics, corticosteroids (for patients without fistulas or abscesses), metronidazole (fistulizing disease), immunosuppressives, methotrexate, and TIBs.

Based both on trials included in the DERP review and more recently published trials, there is fair to good evidence from placebo-controlled RCTs supporting efficacy of infliximab (seven trials) and adalimumab (four trials) for initial and maintenance treatment of Crohn's disease.

There is insufficient evidence to conclude that there are differences in comparative efficacy between infliximab and adalimumab for the treatment of Crohn's disease. Both biologics have published data demonstrating persistence of response for up to one year.

One difference is use in children. Infliximab, but not adalimumab, has published evidence and is indicated for the treatment of pediatric Crohn's disease (ages 6 to 17 years).

Etanercept does not appear to be efficacious for Crohn's disease based on one fair-quality placebo-controlled trial [Sandborn et al, 2001]. The manufacturer states that they have discontinued development of etanercept for this indication. The difference in effect compared to the other two TNF inhibitors may be due to mechanistic differences between the monoclonal antibody agents (adalimumab and infliximab) and the soluble receptor agent etanercept.

g) Ulcerative Colitis

UC is a chronic inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea; fistulas and abscesses do not occur. Treatment includes 5-aminosalicylic acid (enemas or oral), corticosteroids, immunosuppressives (azathioprine), and TIBs.

Infliximab is the only TIB currently FDA-indicated for UC, with evidence from three published placebo-controlled RCTs supporting efficacy. No published RCTs were found for other TIBs in the treatment of UC.

3) Safety and Tolerability

a) Overall Adverse Event Profile

Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported adverse events (AEs) are injection site or infusion reactions (depending on route). With the exception of injection reactions, the overall rate of AEs and the percentage of patients discontinuing treatment due to AEs (3-16%) were typically comparable to placebo. The incidence of AEs does not appear to increase over time.

Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7).

Infusion reactions have the potential to be more serious than injection site reactions; severe acute reactions have been reported in a small percentage of patients (~1%) after infliximab infusions.

b) Rare but Serious Adverse Events

The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. Current evidence focusing on specific serious adverse events is primarily observational.

Black box warnings concerning the risk of serious infections and the need to test for latent tuberculosis (TB) prior to initiating TIB therapy are included in labeling for adalimumab and infliximab; similar information appears in labeling for other TIBs. In general, caution is indicated in patients with chronic infections or a history of recurrent infections, and TIBs should be stopped if the patient develops a serious infection.

Other black box warnings for TIBs include the risk of hepatosplenic T-cell lymphoma with infliximab (reported in young Crohn's disease patients on other immunomodulatory medications) and a list of potentially severe reactions primarily associated with the use of rituximab for conditions other than RA. There are relatively few absolute contraindications for the TIBs. Alefacept is contraindicated in patients with HIV; etanercept is contraindicated in sepsis; and doses of infliximab greater than 5 mg/kg are contraindicated in patients with moderate to severe heart failure.

(i) Serious Infections

The most common serious infection appears to be TB. Observational studies have also reported infections with coccidiomycosis, histoplasmosis, pneumocystis carinii, listeriosis, candida, and Legionella. Evidence from RCTs is limited.

- A meta-analysis [Bongartz et al, 2006] that pooled data from adalimumab and infliximab RA trials (total n >5000) reported a pooled odds ratio for serious infections of 2.0 (95% CI 1.3 to 3.1), with a number needed to harm of 59 (95% CI 39 to 125) over 3 to 12 months.
- A large RCT (n=1084) designed to assess the risk of serious infections with infliximab in RA patients [Westhovens et al, 2006] reported similar rates of serious infections in patients treated with 3 mg/kg infliximab vs. placebo (RR: 1.0; 95% CI 0.3 to 3.1). However, patients treated with 10mg/kg infliximab had a significantly higher rate of serious infections vs. placebo (RR: 3.1 95% CI 1.2 to 7.9).

The DERP review also included five retrospective database analyses and a prospective cohort study that in general supported a higher risk of TB or granulomatous infection in patients treated with etanercept or infliximab compared to unexposed patients; more recently published studies do not add substantial evidence.

When all data are considered, the P&T Committee agreed that there is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo. There is insufficient evidence to draw conclusions about the comparative risk of serious infection.

(ii) Malignancies

The P&T Committee agreed that largely observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed. There is insufficient evidence to draw conclusions about comparative risk.

(iii)Chronic Heart Failure

Evidence concerning the safety of TIBs in patients with chronic heart HF and the effects of TIBs on the development of chronic HF is mixed. Data from two unpublished etanercept RCTs and one published infliximab RCT evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality among chronic HF patients treated with etanercept or infliximab, compared to placebo. However, observational studies have reported *lower* rates of cardiovascular events in RA patients receiving TNF inhibitors compared to those receiving conventional therapy. Caution is indicated.

(iv) Other

All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and

other autoimmune disorders have been reported with etanercept, adalimumab, and infliximab. The relationship among auto-antibody levels, the likelihood of infusion reactions, degree and durability of clinical response, and the development of autoimmune disorders is unclear.

Based on case reports and product labeling, adalimumab, etanercept, and Infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept. Potential effects on hematologic parameters requiring laboratory monitoring include neutropenia with anakinra (neutrophil counts monthly for 3 months, then quarterly for 1 year); dose-dependent reductions in CD4+ T lymphocytes reported with alefacept (CD4+ T lymphocyte counts every 2 weeks during the 12-week treatment period); and periodic assessment of platelet counts with efalizumab (monthly to quarterly).

c) Drug Interactions

There is little substantive information concerning potential drug interactions with the TIBs. They are in general considered safe for use with the large number of drugs used concomitantly in clinical trials.

In general, additive effects on the immune system appear to preclude concomitant treatment with more than one TIB. A trial assessing a combination of anakinra and etanercept (plus MTX) appeared to offer no additional clinical benefit compared to etanercept plus MTX, but resulted in a substantially higher rate of pancytopenia and serious infections. Similarly, a trial assessing the addition of abatacept to etanercept appeared to offer minimal additional clinical benefit compared to etanercept alone, but resulted in a substantially higher rate of adverse events (including serious adverse events and serious infections).

4) Use in Special Populations

Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), although this has not been extensively studied. A higher risk of mortality among chronic HF patients treated with etanercept or infliximab has been previously discussed. Caution is in general indicated in elderly patients due to a higher background risk for serious infections and malignancy.

Other differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C due either to complete lack of data or some evidence of harm in animal studies); the potential for a higher risk of AEs with anakinra in patients with impaired renal function (anakinra is known to be substantially excreted by the kidney; dose reduction is recommended); and the availability of safety and efficacy data in pediatric patients (etanercept is the only TIB FDA-indicated for JRA; infliximab is the only TIB indicated for pediatric Crohn's disease [age 6-17]).

5) Provider Opinion

Opinions of MTF providers familiar with the use of TIBs were solicited through the Army, Navy, and Air Force specialty leaders for the three specialties in which these agents are primarily used (rheumatology, dermatology, and gastroenterology).

- *Rheumatology* – Factors influencing the decision to choose between adalimumab and etanercept were frequency of dosing and the shorter half-life of etanercept, which was considered useful in patients in whom there was a fear of infectious complications. Responders considered the two equally efficacious, and almost universally reported efficacy with a second TIB in patients who had had an inadequate response to the first TIB. They tended to use abatacept, then rituximab, in patients failing TNF agents, usually after a trial of two agents. Anakinra was not considered useful in RA; responders cited anecdotal use in Still's disease (pediatric and adult).
- *Dermatology* – Responders stated that they usually started with etanercept for psoriasis (with which they had the most experience) or adalimumab; many would consider adalimumab after a 4- to 6-month trial of etanercept. Some do use adalimumab as first line. Based on the published data (PASI 75 scores), providers thought that adalimumab might have greater efficacy, although they also theorized that it might have a higher risk of infection based on its binding of both tissue-bound and soluble TNF. Comments about dosing of etanercept (i.e., patients staying on the twice-weekly 50 mg dose after the initial treatment period) included a perception that many patients require the higher dose and that many also require additional therapy (phototherapy, MTX), the possibility that etanercept may need to be weight-based due to higher TNF production in patients with a high BMI; and the perception that effects of etanercept may wane over time, requiring that the dose be increased back to 50 mg twice weekly.

  Survey responders typically placed efalizumab before alefacept in patients with a contraindication to TNF inhibitors or who had failed etanercept or adalimumab. Efalizumab was noted to be helpful when treating very heavy or light-weight individuals, since dosing is weight-based; it was also noted as having a potential role in some off-label uses. Infliximab was typically reserved for severe or refractory disease or for patients in whom a more rapid onset of improvement is necessary (pustular psoriasis); responders noted that cyclosporine and infliximab are really the only options for acute cases.
- *Gastroenterology* – Responders commented that most are now using adalimumab for Crohn's disease to some extent (instead of infliximab); some prefer adalimumab as the first choice because of easier administration. They perceived that many providers will continue to use infliximab due to lack of guidelines. They noted that the factors affecting their choice of biologic agent for Crohn's disease were concerns about infusion reactions, antibody formation, need for a concomitant immunosuppressant, and type of disease

(with more literature and experience with infliximab for the treatment of fistulizing disease).

Responders did not perceive that there was much (off-label) use of adalimumab for Crohn's disease at present, although some providers have commented that they would try it before cyclosporine or colectomy in patients who cannot take infliximab.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusion:

a) Across all disease states reviewed, all of the TIBs FDA-indicated for a particular condition have sufficient evidence from placebo-controlled RCTs to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus MTX offers better efficacy than TIBs or MTX alone. Beneficial effects on QoL and productivity are associated with improvements in clinical response.

b) There is a lack of direct comparative evidence (head-to-head RCTs) across all disease states. In all disease states except RA, trials were too small in number or too heterogeneous to make indirect comparisons based on meta-analysis of placebo-controlled trials feasible. With two exceptions, treatment effect across agents appeared similar.

c) In RA, anakinra appears to be less efficacious than the TNF inhibitors (etanercept, adalimumab, and infliximab) with respect to effects on symptoms (ACR response), based on indirect comparison of data from placebo-controlled trials.

d) In psoriasis, PASI 75 scores for infliximab appeared consistently higher than with other TIBs used for psoriasis (etanercept, alefacept, and efalizumab), although there is insufficient comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials. An indication for adalimumab for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer supports its efficacy for this condition.

e) The multi-indication self-administered TIBs (adalimumab and etanercept) compare favorably to one another. Etanercept did not appear to be efficacious in Crohn's disease, for which adalimumab is indicated. Adalimumab lacks published evidence in JRA and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. For disease states in which both are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.

f) Alefacept and efalizumab are FDA-indicated only for psoriasis; they appear to compare favorably to etanercept in terms of treatment effect. Their place in therapy relative to etanercept and infliximab (and potentially adalimumab) in the treatment of psoriasis is probably dependent on factors such as intramuscular administration of alefacept, recommended lab monitoring with both agents, and greater familiarity of providers with the TNF inhibitors.

g) Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported AEs are injection site or infusion reactions (depending on route). Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7). In addition, anakinra is given once daily, as opposed to weekly or every other week dosing for adalimumab and etanercept.

h) The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. There is insufficient evidence to draw conclusions about comparative risk of any of these serious AEs.

   i) There is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo.

   ii) Observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed.

   iii) Evidence concerning the safety of TIBs in patients with chronic HF and the effects of TIBs on the development of chronic HF is mixed. Data from etanercept and infliximab RCTs evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality compared to placebo. However, observational studies have reported *lower* rates of cardio-vascular events in RA patients on TNF inhibitors compared to those on conventional therapy.

   iv) All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other autoimmune disorders have been reported with etanercept, adalimumab, and infliximab.

   v) Adalimumab, etanercept, and infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept.

vi) Laboratory monitoring is required or recommended for anakinra (neutrophil counts), alefacept (CD4+ T lymphocyte counts), and efalizumab (platelet counts) due to reports of hematologic abnormalities.

i) There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concomitantly in clinical trials. Based on two combination trials (one with anakinra plus etanercept and one with abatacept plus etanercept), additive effects on the immune system appear to preclude concomitant treatment with more than one TIB.

j) Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), with the exception of a reported higher risk of mortality among chronic HF patients treated with etanercept or infliximab. Potential differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C); the need for dose reduction of anakinra in patients with impaired renal function; and availability of data in pediatric patients (etanercept for JRA; infliximab for pediatric Crohn's disease).

B. TIBs – Relative Cost Effectiveness –The P&T Committee evaluated the relative cost effectiveness of the TIBs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The TIBs were grouped into sub-groups according to the number of indications for treatment that each agent possessed. The multi-indication agents included etanercept and adalimumab, and the single-indication agents consisted of anakinra, efalizumab, and alefacept. The cost effectiveness review compared the estimated cost of treatment by disease state for RA and plaque psoriasis. For RA, the analysis compared etanercept, adalimumab, anakinra, and infliximab, while the analysis of plaque psoriasis compared efalizumab, etanercept, and alefacept. Although infliximab is not part of the pharmacy benefit (it is covered under the TRICARE medical benefit), it was included in the analysis because it has indications for treatment that are similar to the products evaluated for the TIBs cost effectiveness review.

The relative clinical effectiveness evaluation concluded that the TIBs are effective for the treatment of RA and plaque psoriasis. Moreover, there was insufficient evidence to suggest that the TIBs' treatment effectiveness differed for RA and plaque psoriasis with one exception: Anakinra appeared to be less effective for the treatment of RA than the multi-indication TIBs, based on the available evidence.

With this information, a cost analysis for RA was conducted to compare the expected cost per year of treatment for each drug product by indication across all three points of service. Results from the analysis showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar clinical effectiveness, while anakinra was the most costly agent evaluated and

was less effective than the multi-indication TIBs. The results showed that neither etanercept nor anakinra were cost effective when compared to adalimumab for the treatment of RA, and the conclusions were robust to assumptions about dose escalation with adalimumab. In the analysis of plaque psoriasis, all three products evaluated had comparable cost effectiveness profiles.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., condition sets, market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of multi-indication TIBs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS. The results showed that the scenario where adalimumab was the sole multi-indication TIB on the UF was the most cost effective scenario evaluated in the BIA.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) For RA, the clinical effectiveness evaluation concluded that anakinra appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for etanercept, adalimumab, and anakinra showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar effectiveness, while anakinra was both more costly and less effective.
2) For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for efalizumab, etanercept, and alefacept showed similar cost effectiveness profiles for all three agents.
3) The UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the TIB relative cost effectiveness analysis as presented by the PEC. The Committee concluded that the UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective UF scenario.

C. TIBs – UF Recommendation

COMMITTEE ACTION: Taking into consideration the relative clinical effectiveness and relative cost effectiveness conclusions for the TIBs and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 2 opposed, 1 abstained, and 1 absent) to recommend that adalimumab, efalizumab, and alefacept be maintained as formulary on the UF and that etanercept and anakinra be classified as non-formulary under the UF.

D. TIBs – MN Criteria

Based on the clinical evaluation for etanercept and anakinra, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for etanercept and anakinra:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Formulary agents have resulted or are likely to result in therapeutic failure.
4) Patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
5) (Etanercept only) There is no formulary alternative.

With respect to criterion #4, the P&T Committee's primary concern was for patients stabilized on treatment with etanercept or anakinra.

With respect to criterion #5, the P&T Committee agreed that this in general applies only to etanercept, as multiple formulary alternatives are available for anakinra, which is FDA-indicated only for RA. Etanercept is currently the only TIB indicated for JRA; the other self-administered multi-indication TIB, adalimumab, lacks an indication for plaque psoriasis.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. TIBs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for their TIB. A retrospective pharmacy claims analysis revealed that approximately 11,500 DoD beneficiaries have filled a prescription for a non-formulary TIB in the previous quarter.

MTFs will not be allowed to have etanercept or anakinra on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for non-formulary TIB written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately

following the approval by the Director, TMA. The P&T Committee also recommended that letters be sent to educate patients receiving non-formulary TIBs about the change in formulary status.

F. TIBs – PA Requirements, Criteria, and Implementation Period

Currently PA requirements apply to etanercept, adalimumab, anakinra, and efalizumab. A PA is not currently required for alefacept. The P&T Committee agreed that the following PA criteria should apply to alefacept, consistent with FDA-approved labeling and PA requirements for the other TIBs, and with an implementation period consistent with that established for the UF decision in this class.

1) Coverage would be approved for the treatment of:
   - Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy

2) Coverage would NOT be approved for:
   - Patients with HIV, patients with a CD4+ T lymphocyte count below normal at start of treatment, immunocompromised patients or those receiving other immunosuppressive agents or phototherapy
   - Children (age < 18 years)

Current PA criteria for etanercept, adalimumab, anakinra, and efalizumab are outlined in Appendix C. The P&T Committee agreed that the PA criteria reflect current FDA labeling and published clinical literature and require no substantive changes. Minor changes to clarify wording and increase consistency, as well as possible future changes to accommodate new FDA indications, will be accomplished on an administrative basis.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to PA criteria for etanercept, adalimumab, anakinra, and efalizumab as outlined in Appendix C; 2) that a PA be required for alefacept under the PA criteria outlined above; and 3) that the effective date for the alefacept PA be timed to coincide with that established for the UF decision in this class.

G. TIBs – QLs

Currently, quantity and/or days supply limits apply to etanercept, adalimumab, and anakinra, as outlined in Appendix C. In general, patients are limited to a 4-week supply of these medications at retail network pharmacies at any one time (no multiple fills for multiple copays) and a 6- to 8-week supply at the TMOP, based on product labeling and packaging. The intent is to limit potential wastage if medications are discontinued or changed.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to existing quantity / days supply limits for etanercept, adalimumab, and anakinra.

H. TIBs – Extended Core Formulary (ECF) Review and Recommendations – Based on the results of the clinical and economic evaluations presented, the P&T Committee

voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that adalimumab be added to the ECF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that adalimumab be added to the ECF.

9. BCF STATUS OF ROSIGLITAZONE

At the P&T Committee's request, the PEC updated the Committee on the latest news/evidence regarding the safety of thiazolidinedione (TZD) agents, particularly that of rosiglitazone (Avandia), the DoD's BCF TZD. The PEC informed the Committee about recent changes in DoD TZD utilization, evidence (meta-analyses, systematic reviews, and clinical studies) that has emerged in the clinical literature since the last meeting, and a revision to an FDA Alert for rosiglitazone issued 21 May 2007.

The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone and rosiglitazone/metformin (Avandamet) from the BCF. Ultimately, the P&T Committee determined that there was sufficient clinical evidence to justify removal of rosiglitazone and rosiglitazone/metformin from the BCF.

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to remove rosiglitazone and rosiglitazone/metformin from the BCF at this time.

10. BCF / ECF REVIEW

As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in two current BCF drug classes, analgesics (meloxicam , cyclobenzaprine, and oxycodone/acetaminophen) and ADHD and narcolepsy agents (methylphenidate IR). Details are outlined in Appendix D.

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings as outlined in Table 4 (see Appendix D for rationale):

Table 4. Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Analgesics	BCF – Meloxicam (Mobic) oral	Clarify BCF listing to "meloxicam tablets only"	14	0	1	2
	BCF – Cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	Clarify BCF listing to "cyclobenzaprine IR tablets, 5 and 10 mg"	14	0	1	2
	BCF – Oxycodone 5 mg / acetaminophen 325 mg	Clarify BCF listing to "oxycodone 5 mg / acetaminophen 325 mg tablets"	14	0	1	2
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	Clarify BCF listing to "methylphenidate IR (excludes Methylin oral solution and chewable tablets), methylphenidate ER (specific brand name is Concerta); mixed amphetamine salts ER (Adderall XR)"	14	0	1	2

11. RE-EVALUATION OF AMLODIPINE'S UF STATUS

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. At this meeting, the UF status of amlodipine (Norvasc, generics) was re-evaluated due to a significant decrease in cost across all three points of service.

In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc. Until recently, the price for amlodipine, even though available generically, was similar to the price for brand name Norvasc and did not support a change in its UF status.

At the August 2005 P&T Committee meeting, the Committee concluded that in general, amlodipine had similar clinical effectiveness relative to other DHP CCBs in regards to efficacy, safety, and tolerability. In consideration of the Committee's previous relative clinical effectiveness conclusion, a CMA was performed to determine the cost effectiveness of amlodipine relative to the other DHP CCBs included on the UF. The results of the CMA showed amlodipine to be the most-cost effective DHP CCB.

Cost Effectiveness Conclusion – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the relative CEA as presented by the PEC.

A. Amlodipine – UF Recommendation

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that amlodipine be reclassified as formulary on the UF.

B. Amlodipine – UF Implementation Period

The P&T Committee recommend immediate implementation upon signing of the November 2007 DoD P&T Committee minutes by the Director, TMA.

COMMITTEE ACTION: The P&T Committee recommend (15 for, 0 opposed, 1 abstained and 1 absent) an effective date as the date the Director, TMA signs the minutes.

C. Amlodipine – BCF Review and Recommendation

COMMITTEE ACTION: The P&T Committee considered the BCF status of the DHP CCB agents. Based on the results of the clinical and economic evaluations presented, the Committee voted (15 for, 0 opposed, 1 abstained and 1 absent) to add amlodipine to the BCF.

12. RE-EVALUATION OF NON-FORMULARY AGENTS

The P&T Committee's process for the re-evaluation of non-formulary agents established at the May 2007 meeting was approved by the Director, TMA on 24 June 2007. For this meeting, the PEC applied the appropriate criteria and defined a list of non-formulary drug agents for re-evaluation of UF status (Table 5) for the P&T Committee's consideration. More specifically, the non-formulary agents identified for re-evaluation were: 1) from

drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF and not excluded from the UF based on clinical issues alone.

Table 5 – Non-Formulary Agents for Re-Evaluation

Generic Name	Brand Name	UF Class	Generics Shipping
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
quinapril	Accupril	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan /Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N

Accordingly, the PEC recommended that the following pre-established criteria be applied to each non-formulary agent for re-evaluation of UF status.

1) The non-formulary agent becomes generically available and:

   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system

   b) The generic market supply is stable and sufficient to meet MHS supply demands.

2) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost effective when:

   c) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

   d) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF

class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

The PEC reminded the DoD P&T Committee that when the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.

1) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
2) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

The P&T Committee developed the process for the re-evaluation of non-formulary agents for UF status because it recognized that there are situations in which it would be helpful if a procedure were in place that allowed reclassification of a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 1 absent) to recommend that the above list of non-formulary drug agents be re-evaluated for UF status when pre-established criteria are met.

13. CLASS OVERVIEWS

The class overview for the Pulmonary-1 Agents was presented to the P&T Committee. This drug class comprises the short-acting beta agonists, long-acting beta agonists (LABA), inhaled corticosteroids, and corticosteroid/LABA combinations.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the relative clinical effectiveness evaluation and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed for a future meeting; no action is necessary.

14. ADJOURNMENT

The second day of the meeting adjourned at 1530 hours on 15 Nov 2007. The next meeting will be 12-13 Feb 2008.

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Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	Pending approval	Pending approval
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin ER tablets (Uroxatral)	Pending approval	Pending approval
Nov 07	Adrenergic Beta-Blocking Agents	-	BCF	▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	Pending approval	Pending approval
Nov 07 (update, original review Aug 05)	Calcium Channel Blockers	**Currently non-formulary, recommended for UF status Nov 07** ▪ amlodipine (Norvasc generic)	BCF	**Recommended for addition to BCF Nov 07** ▪ amlodipine besylate tablets	Pending approval	-
		To Remain Non-Formulary ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently on the BCF ▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	-	Pending approval	Pending approval
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	-	Pending approval	Pending approval

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Nov 07 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Nov 07** ▪ valsartan/amlodipine (Exforge)	BCF	-	Pending approval	Pending approval
		To remain NF ACE inhibitors ▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Leukotriene Modifiers	▪ zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
Aug 07 (new drug update, original review Nov 05)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended for non-formulary status Aug 07 ▪ fluticasone furoate (Veramyst)			17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (updated Nov 07)	ADHD / Narcolepsy Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	-
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated Nov 06, Nov 07)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended for non-formulary status Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)		-	17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05 (re-review Nov 07)	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05 (updated Nov 07)	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
		Recommended for non-formulary status Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle
ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs= Thiazolidinediones
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. November 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Formoterol fumarate inhalation solution (Perforomist, Dey) inhaled LABA	May 07 (launched Oct 07) Long term twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. Not intended to treat asthma or acute deterioration of COPD	No UF recommendation at this meeting. Consideration of UF status deferred until inhalational Pulmonary I drugs are reviewed; UF review anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o #180 unit dose vials per 90 days ▪ Retail Network o #60 unit dose vials per 30 days

Appendix C – Existing Prior Authorization Criteria and Quantity Limits for Targeted Immunomodulatory Biologics

	Adalimumab (Humira)	Etanercept (Enbrel)	Anakinra (Kineret)	Alefacept (Amevive)	Efalizumab (Raptiva)
Prior Authorization (approved PAs are good indefinitely)	Coverage provided for the treatment of: ▪ Moderately to severely active RA in patients 18 years of age or older. ▪ Active arthritis in patients with PsA 18 years of age or older. ▪ Active AS in patients 18 years of age or older. ▪ Moderately to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to infliximab, or an inability to tolerate infliximab in patients 18 years of age or older. ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	Coverage provided for the treatment of: ▪ Moderately to severely active RA ▪ Active PsA ▪ Active AS ▪ JRA when the patient has an inadequate response to at least one DMARD ▪ Chronic moderate to severe plaque psoriasis when the patient has tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR is not a candidate for phototherapy or systemic therapy ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	Coverage provided for the treatment of: ▪ Moderately to severely active RA in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD). ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	none	Coverage provided for the treatment of: ▪ Adults (age = 18 years) with chronic moderate to severe plaque psoriasis, defined as a minimum body surface area involvement of 10% OR a body surface area involvement of less than 10%, but in critical areas (e.g. palms, soles or face) and interfering with day-to-day activities AND ▪ who have tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR are not candidates for phototherapy or systemic therapy AND ▪ for whom a dermatologist recommends treatment. Coverage NOT provided for: ▪ Immunocompromised patients or those receiving immunosuppressive agents. ▪ Children (age < 18 years) ▪ Patients with PsA without plaque psoriasis
Quantity Limits	Maximum quantity dispensed at any one time: 4 weeks supply (2 packs of 2 syringes) in retail and 6 weeks supply (3 packs of 2 syringes) in mail order. Does not apply to the Crohn's Disease starter pack (6 pens for the first 4 weeks of treatment), which is limited to 1 package (6 pens), with no refills.	4-week supply in retail and a 6-week supply in mail order (based on instructions for use on the prescription)	Maximum quantity dispensed at any one time is 4 weeks supply (1 package of 28 syringes) in retail and 8 weeks supply (2 packages of 28 syringes) in mail order		

Appendix D– Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF / ECF listing	Recommendation/ Rationale
Analgesics	BCF – meloxicam (Mobic) oral	• In Aug 2002, meloxicam (Mobic) tablets were added to the BCF • All tablets are now available in generic formulations • In June 2004 the FDA approved Mobic suspension 7.5 mg/ 5 ml (no generics available) • In the last year, there have been 30 Rxs across all Points of Service • Recommendation: • Clarify BCF listing to "meloxicam tablets only"
	BCF – cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	• In Nov 2003, cyclobenzaprine was clarified to exclude the 5 mg strength due to high cost and availability solely as proprietary Flexeril • All IR products are now available in generic formulations at a cost of ~$0.02/tab • A new cyclobenzaprine ER capsule, Amrix (Cephalon), entered the market in Feb 2007 • Recommendation: • Clarify BCF listing to "cyclobenzaprine IR tablets, 5 and 10 mg"
	BCF – oxycodone 5 mg / acetaminophen 325 mg	• The BCF listing does not clarify tablets or capsules and does not specify the 5 mg / 325 mg product • No capsules are available in this strength • Recommendation • Clarify BCF listing to "oxycodone 5 mg / acetaminophen 325 mg tablets"
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	• The methylphenidate IR oral tablets are available in generic formulations, and are listed on the PEC website as a BCF item. • The Nov 06 P&T Committee minutes for the ADHD BCF drugs were ambiguous for methylphenidate IR oral solution and chewable tablets, available under the brand name Methylin. These Methylin formulations are the only IR products available for the oral solution and chewable tablets. • The Uniform Formulary search tool BCF listing was erroneous, and the manufacturer of Methylin solution and chewable tablets concluded their products were BCF items. • Since Oct 06, MHS utilization for Methylin has been low, at 7 Rx's dispensed monthly for the solution and 4 Rx's dispensed monthly for the chewable tablets. • A CMA found that Methylin solution and chewable tablets were less cost effective than other methylphenidate IR formulations. • Recommendation: • Clarify BCF listing for ADHD drugs to exclude Methylin oral solution and chewable tablets.

Appendix E – Table of Abbreviations

AB	Alpha Blocker (drug class)
ABA	Adrenergic Beta Blocker (drug class)
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
AS	ankylosing spondylitis
ARB	angiotensin receptor blocker
AUA-SI	American Urological Association Symptom Index
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BP	blood pressure
BPH	benign prostatic hypertrophy
CCB	calcium channel blocker
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CMA	cost minimization analysis
CR	controlled release (extended release)
DERP	Drug Effectiveness Review Project (State of Oregon)
DHP	dihydropyridine
DMARD	disease-modifying antirheumatic drugs
DoD	Department of Defense
EE	ethinyl estradiol
ER	extended release
FDA	Food and Drug Administration
FY	fiscal year
HCTZ	hydrochlorothiazide
HF	heart failure
IFIS	intraoperative floppy iris syndrome
IPSS	international prostate symptom score
IL	interleukin
IR	immediate release
JRA	juvenile rheumatoid arthritis
LABA	long-acting beta agonists
LUTS	lower urinary tract symptoms
M20 EE	monophasic contraceptive with 20 mcg ethinyl estradiol
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	military treatment facility
MTX	methotrexate
NSR	normal sinus rhythm
PA	prior authorization
PASI	Psoriasis Area and Severity Index
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PDE-5	Phosphodiesterase type 5
PsA	psoriatic arthritis
Pulm I	Pulmonary I (drug class)
QD	once daily

Appendix E – Table of Abbreviations (continued)

Qmax	urinary flow rate
QoL	quality of life
RAAs	renin-angiotensin antihypertensive (drug class)
RCT	randomized controlled trial
RR	relative risk
TB	tuberculosis
TIBs	Targeted Immunomodulatory Biologics
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TNF-α	Tumor Necrosis Factor alpha
TRRx	TRICARE Retail Pharmacy Network
UC	ulcerative colitis
UF	Uniform Formulary
XR	extended release

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2007

1) **CONVENING**
2) **ATTENDANCE**
3) **REVIEW MINUTES OF LAST MEETING**
4) **ITEMS FOR INFORMATION**
5) **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The P&T Committee was briefed on four new drugs which were approved by the U.S Food and Drug Administration (FDA) (see Appendix B). The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) requirements for budesonide/formoterol (Symbicort) oral inhaler. (See paragraph 5A on page 20 of the P&T Committee minutes).

COMMITTEE ACTION: QUANTITY LIMITS – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/ formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

Background – In May 2007, the P&T Committee re-classified the angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), ARB/calcium channel blockers combinations and any newly approved antihypertensive drugs affecting the renin system into a single drug class, the Renin-Angiotensin Antihypertensives (RAAs). Aliskiren is the first new drug in the RAA class.

Relative Clinical Effectiveness Conclusion – the P&T Committee voted (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated below. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

a) Aliskiren is a new antihypertensive agent with a novel mechanism of action as a direct renin inhibitor.

b) Aliskiren's blood pressure (BP) lowering effects are similar to those achieved with other antihypertensives, but it does not show improved efficacy compared to other classes of antihypertensive agents.

c) Combination therapy of aliskiren with ACE inhibitors, diuretics and ARBs has shown additive BP lowering effects compared to monotherapy with other antihypertensive agents.

d) Several other safe, once-daily, less costly antihypertensive drugs are available that have proven clinical outcomes (e.g., ACE inhibitors, ARBs, diuretics).

e) The long-term adverse event profile of aliskiren is unknown; diarrhea is the most commonly reported adverse event and the discontinuation rate is similar to placebo.

f) Clinical outcomes of aliskiren are unknown. Trials are underway, with initial results anticipated in November 2007.

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

Although aliskiren was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren non-formulary at this time given its novel mechanism of action and the anticipated availability of clinical outcomes data that would enable the P&T Committee to more definitively assess its value relative to other anti-hypertensives.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be classified as formulary on the UF. The four opposing votes were cast due to the opinion that there was insufficient evidence to recommend formulary placement; the one abstaining vote was due to the opinion that there was a lack of sufficient cost effectiveness compared to the ARBs. (See paragraph 5B on pages 20-23 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: "On condition that active surveillance be initiated."

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

Background – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005; fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and flunisolide (Nasarel) were designated as formulary on the UF, while beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA) were classified as non-formulary. Fluticasone furoate is a new nasal corticosteroid that replaces the

propionate ester of fluticasone propionate with a furoate ester. *In vitro* claims of enhanced glucocorticoid receptor binding *in-vitro* have not translated into enhanced clinical effectiveness.

There is insufficient evidence to determine if there are clinically relevant differences between Veramyst and Flonase; one head-to-head trial in patients older than 12 years of age with SAR showed that Veramyst was not inferior to Flonase in terms of changes from baseline in Total Nasal Symptom Score. Veramyst's adverse effect profile appears similar to other nasal corticosteroids. The P&T Committee also evaluated differences in the delivery device, ease of administration, and particle size of Veramyst compared to other nasal corticosteroids, but did not find a unique advantage or disadvantage relative to fluticasone propionate or mometasone furoate.

Relative Clinical Effectiveness Conclusion: The DoD P&T Committee concluded (12 for, 0 opposed, 1 abstained, 4 absent) that:

> Fluticasone furoate has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other nasal corticosteroids included on the UF.

Relative Cost Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

> Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF. (See paragraph 5C on pages 23-25 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** – Based on the clinical evaluation of fluticasone furoate and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the nasal corticosteroids. (See paragraph 5C on page 26 of the P&T Committee minutes for the criteria).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an

effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy (TRRx) network, and at military treatment facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TRICARE Management Activity (TMA). Committee members directed that if operationally feasible, the $22 co-pay should start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current fluticasone furoate users. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

4) ***COMMITTEE ACTION: QUANTITY LIMITS*** - The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend a QL for fluticasone furoate in the TRRx of 1 inhaler device per 30 days and a QL in the TMOP of 3 inhaler devices per 90 days. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

6) DRUG CLASS REVIEW – NEWER ANTIHISTAMINE (NA) DRUG CLASS

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents: loratadine (Claritin, generics), acrivastine/ pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. As of June 2007, about three million Military Health System (MHS) prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 .

The brand-only agents in this class are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for a very recently approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

1) Based on randomized placebo-controlled trials, cetirizine, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR and CIU. Acrivastine/pseudoephedrine is more efficacious than placebo for the symptomatic relief of SAR.

2) Based on six comparative trials in adults with SAR, there is insufficient evidence to suggest that there are clinically significant differences between cetirizine, fexofenadine, and loratadine, or desloratadine and fexofenadine. There is insufficient evidence to compare any of the agents in children less than 12 years old with this condition.
3) For the treatment of PAR in adults, there is insufficient evidence to suggest clinically significant differences between the agents. In children 2 to 6 years old, limited evidence based on one fair/poor quality comparative trial suggests that cetirizine may be more efficacious than loratadine with PAR.
4) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.
5) The NAs appear to have similar adverse effect profiles and to result in similar low rates of discontinuation due to adverse events in clinical trials. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions.
6) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.
7) All the parent products have multiple dosage forms and a pseudoephedrine-containing combination product.
8) It is likely that at least one NA is needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.
9) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

Cost Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Desloratadine and desloratadine/pseudoephedrine were not cost effective relative to other comparable agents in the newer antihistamine class.
2) The UF scenario that placed desloratadine and desloratadine/pseudoephedrine as non-formulary was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to

recommend the following. (See paragraph 6C on page 33 of the P&T Committee minutes.)

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/ pseudoephedrine , and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available OTC, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for desloratadine and desloratadine/pseudoephedrine, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for desloratadine and desloratadine/pseudoephedrine. (See paragraph 6D on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and no longer than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 6E on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and

2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single ingredient agent from the NA class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. (See paragraph 6F on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7) DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LM agents. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available.

Currently montelukast is the only BCF LM agent. None of the LMs are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) to accept the following clinical effectiveness conclusion:

a) For the treatment of asthma, National Heart, Lung and Blood Institute National Asthma Education Prevention Program guidelines include LMs as an alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than inhaled corticosteroids (ICS), and are less effective when added on to long-acting beta agonist (LABA) vs. use of a LABA with ICS. Addition of a LM to ICS provides modest benefit over use of the ICS as monotherapy.

b) In placebo-controlled trials for asthma, the three LMs montelukast, zafirlukast, and zileuton demonstrate clinical effectiveness in endpoints such as reduction in exacerbations, improvements in forced expiratory volume in 1 second (FEV1), asthma symptoms scores and short acting beta-agonist use. There is insufficient evidence to determine whether one LM is more efficacious at controlling asthma symptoms than another.

c) Limited evidence suggests that LMs may permit a reduced ICS dose, or could be used in patients resistant to or unable to tolerate inhaled steroids. The extent or clinical significance of this "steroid sparing" effect is uncertain.

d) Montelukast is the only LM that is FDA approved for the treatment of allergic rhinitis (AR), and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of allergic

rhinitis, but they fail to consistently show efficacy. There is no data to support the use of zileuton in AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR endpoints such as rhinitis symptom scores and rhinoconjunctivitis quality of life scores; however, the treatment effect is modest. When compared to antihistamines, the LMs show relatively similar efficacy. Nasal corticosteroids (NCS) are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine are modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

f) In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

g) In regard to safety and tolerability, zileuton has been associated with hepato-toxicity, requires liver function test monitoring, and is contraindicated in patients with active liver disease. Zafirlukast has also been associated with hepatotoxicity including liver failure and death; however, this data is from spontaneously reported adverse event reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

h) In regard to other factors, montelukast has the advantage of a greater number of FDA approved indications, pediatric indications, less frequent dosing (once daily versus twice and four-times daily for zafirlukast and zileuton), and availability of alternative dosage formulations.

i) Overall, based on clinical issues alone, montelukast is preferred over zafirlukast, which in turn is preferred over zileuton.

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, and 2 absent) that:

a) Zafirlukast was the least costly agent in the class; montelukast was more costly relative to zafirlukast but provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class; zileuton was not cost effective relative to the other products.

b) LMs are not cost effective in the treatment of AR relative to antihistamines and nasal corticosteroids and should not be considered as first-line therapy in the treatment of AR.

c) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/prior authorization (PA) program required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

A. COMMITTEE ACTION: STEP THERAPY RECOMMENDATION – Although the committee agreed that the LMs are not cost effective for AR, the Committee

voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required. (See paragraph 7C on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: "ASD(HA) urges that these patients be followed re: possible CV +/or oncologic benefits or AE's."

B. ***COMMITTEE ACTION: UF RECOMMENDATION*** – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF. (See paragraph 7D on page 43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for zileuton and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for zileuton. (See paragraph 7E on pages 43-44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and no later than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 7F on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules). (See paragraph 7G on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8) DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

This class of drugs includes only two molecular entities, somatropin and mecasermin. There are multiple competing somatropin products. The majority of these are indicated for the treatment of GH deficiency (GHD), which is the most common use. Mecasermin is an orphan drug approved by the FDA in 2005 to treat severe primary insulin-like growth factor deficiency (IGFD), which affects a very small number of patients (about 6,000 in the United States).

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

a) Somatropin products appear to be safe and efficacious for the treatment of various growth-related conditions and for a few specialized non-growth related conditions.

b) There are no studies comparing any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human GH, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

c) There are potential differences between somatropin products with respect to delivery devices, formulations, and stability/storage requirements. Differences that may favor particular products include availability of a pen device (preferably along with a vial/syringe product); the ability to use the pen device without having to do dose conversions, and the ability to store products at room temperature before or after initial use.

d) Mecasermin is safe and efficacious for severe IGFD, a much rarer condition than GHD. It is the only product available for the treatment of this condition.

e) Based on clinical issues alone, there are no compelling reasons to classify any of the GSA agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (15 for, 0 opposed, 0 abstained, and 2 absent) that:

a) Mecasermin (Increlex) and two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and offer sufficient value on a cost/mg basis relative to the other agents within the therapeutic class.

b) Tev-Tropin was the most cost effective somatropin agent based on cost minimization analysis. However, the product offers fewer features than most other growth stimulating agent product lines.

c) Two somatropin product lines, Norditropin and Nutropin, offered more features (pen dosage forms, storage at room temperature, and ease of use) at a middle range of cost.

d) The budget impact analysis results showed that the most cost effective formulary strategy for the somatropin products was the combination of the Tev-Tropin and the Norditropin and Nutropin product lines.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the GSAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that Tev-Tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and Increlex be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary under the UF. (See paragraph 8C on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope. (See paragraph 8D on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8E on pages 57-58 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: PA CRITERIA – Currently, PA criteria apply to both GH (somatropin products) and mecasermin (Increlex). The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) PA criteria for GH (somatropin products) and mecasermin (Increlex). Changes from previous GH (somatropin) criteria are the addition of Noonan's Syndrome and Short Stature Homeobox gene (SHOX) deficiency as covered uses; no changes were recommended to mecasermin criteria. (See paragraph 8F on pages 58-59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin and Norditropin / Nordiflex be added to the ECF. (See paragraph 8G on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9) QUANTITY LIMITS

A. COMMITTEE ACTION: QL FOR RIZATRIPTAN (MAXALT) – The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 12 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 9A on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10) BCF STATUS OF ROSIGLITAZONE

The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone (Avandia). The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more

information becomes available. (See paragraph 10 on pages 59-60 of the P&T Committee minutes.)

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to retain rosiglitazone on the BCF at this time.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11) BCF / ECF REVIEW

The P&T Committee agreed with a plan to systematically review drug classes represented on the BCF and ECF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate / vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine).

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings. (See paragraph 11 on page 60 of the P&T Committee minutes and Appendix C).

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Implementation Status of UF Recommendations/Decisions
Appendix B – Newly Approved Drugs
Appendix C – BCF Review
Appendix D – Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____// signed // _____

S. Ward Casscells, III, M.D.
17 October 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
August 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14-15 Aug 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrelló, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician Alternate
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Karl R. Kerchief, MC	Army, Family Practice Physician
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Major Pete Trang, BSC, USAF	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
LTC Chris Conrad, MC, USA	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Todd Semla, Pharm.D.	VAPBM
Bill Coffenberry	TMA Contracting
Brenda Agner	TMA Contracting
Beth Spearman	TMA/POD
CDR Michael J. Contos	USPHS, IHS

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of May Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the May 2007 DoD P&T Committee meeting on 24 July 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss briefed the members of the P&T Committee regarding the June 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Status of Newer Sedative Hypnotic Agents (SED-1) Step Therapy Program – The PEC briefed the members of the P&T Committee on a preliminary analysis of the SED-1 Step Therapy Program. The analysis examined the first week of SED-1 transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 23,790 patients submitted a prescription for a SED-1. A total of 1,592 patients had claims stopped by the Step Therapy Program's automated profile review (APR) process. Of these patients, 771 (48%) subsequently received a SED-1 prescription through 10 August. This represents a window as short as 3 days and is unlikely to be a fair assessment of the Step Therapy Program; the PEC will continue to monitor as more data becomes available. Of patients who subsequently received a SED-1 prescription, 576 (75%) received the preferred product, Ambien IR.

D. Status of Fentanyl Patch Safety Program/Prior Authorization (PA) - The PEC briefed the members of the P&T Committee on a preliminary analysis of the Fentanyl Patch Safety Program. The analysis examined the first week of fentanyl patch transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 2,732 patients submitted a fentanyl patch prescription. A total of 314 patients had claims stopped by the APR process. Of these patients, 255 (81%) subsequently received a fentanyl patch prescription and 59 (19%) did not, through 10 August (minimum 3-day window). Approximately 11% of patients (314/2732) were affected by the Fentanyl Patch Safety Program.

E. Administrative Actions – Modification of Medical Necessity (MN) Criteria for Duloxetine (Cymbalta) and Pregabalin (Lyrica) – Both of these medications recently gained U.S Food and Drug Administration (FDA) approval for new indications: duloxetine for the treatment of generalized anxiety disorder (February 2007) and pregabalin for the treatment of fibromyalgia (June 2007). MN criteria for these two non-formulary medications are interrelated, since duloxetine also has clinical evidence supporting efficacy in fibromyalgia. The PEC obtained input from members of the P&T Committee regarding the best way to make changes to the MN criteria for these two medications. Changes to MN criteria will be made administratively.

- *Duloxetine for Generalized Anxiety Disorder (GAD)* – Current duloxetine MN criteria allow for the use of the non-formulary serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine in patients treated for depression or other psychiatric illnesses who require treatment with an SNRI (e.g., due to failure of selective serotonin reuptake inhibitor [SSRI] therapy) and who have failed an adequate trial, been unable to tolerate, or have contraindications to the SNRI venlafaxine, which is on the UF. Both venlafaxine and duloxetine are FDA-approved for the treatment of GAD; other medications are FDA-approved either for GAD (e.g., paroxetine, escitalopram) or anxiety in general (e.g., buspirone, lorazepam, alprazolam), or have clinical evidence supporting their use (e.g., sertraline). Based on the results of one head-to-head trial [Hartford et al, 2007] and indirect evidence from placebo-controlled trials with duloxetine and venlafaxine, there is insufficient evidence to conclude that either agent is safer or more efficacious for the treatment of GAD; more clinical evidence is available for venlafaxine. Accordingly, the P&T Committee agreed that the MN criteria were adequate as stated.
- *Pregabalin for Fibromyalgia* – Fibromyalgia is a poorly understood, multifactorial condition that is diagnosed based on a history of widespread pain (bilateral, upper & lower body, spine) and often accompanied by fatigue, difficulty sleeping, and depression. American College of Rheumatology (ACR) criteria, which are based on the presence of excessive tenderness on applying pressure to 11 of 18 specific muscle-tendon sites, appear to be about 85% sensitive and specific for fibromyalgia. Prevalence in the U.S. is about 2% (3.4% women, 0.5% men).

  A 2004 American Pain Society guideline advises a stepwise approach to the treatment of fibromyalgia, including early evaluation and treatment of comorbid conditions (e.g., mood and sleep disturbances), an exercise program, and cognitive behavior therapy. The recommended sequence of drug treatment corresponds to the strength of clinical evidence available to guideline authors. It includes an initial trial of a low-dose tricyclic antidepressant (TCA) or cyclobenzaprine (a muscle relaxant structurally similar to the TCAs), which are considered to be supported by strong clinical evidence, followed by subsequent trials of SSRIs, SNRIs, or tramadol (modest evidence), and possible consideration of combination therapy or use of an anticonvulsant. None of these medications are FDA-approved for the treatment of fibromyalgia; pregabalin is the first medication with this FDA indication.

  Clinical trials evaluating pregabalin for the treatment of fibromyalgia include four randomized controlled trials (RCTs) and three open-label studies (based on information supplied by the manufacturer). One 14-week trial (n = 1077) compared three doses of pregabalin (300, 450, or 600 mg/d) to placebo for 14 weeks, resulting in a significant reduction in the mean pain score of about 1 point on an 11-point scale (0-10) compared to placebo [300 mg/d -0.71; 450 mg/d -0.98; 600 mg/d -1.00]. Withdrawals due to adverse effects were substantially higher with pregabalin than placebo and appeared to be dose-related [300 mg/d 16%; 450 mg/d 22%, 600 mg/d 26%; placebo 12%). Pregabalin was also

compared to placebo in a 6-month randomized withdrawal study (n=566). Significantly more patients on placebo had lost clinical response at endpoint (61%) compared to those on pregabalin (32%). The other two trials consist of a 13-week RCT, which reported about a 0.7 point reduction in endpoint mean pain score with 600 mg/d of pregabalin, compared to placebo ($p<0.05$), and an 8-week trial comparing 150-, 300-, or 450 mg/d of pregabalin to placebo that showed a significant reduction in mean pain score only for the 450 mg/d dose. The latter was not included as part of the FDA approval process; it is the only trial currently published [Crofford et al, 2006].

A small (n=75) placebo-controlled 12-week RCT evaluating gabapentin (a formulary anticonvulsant medication similar to pregabalin) for the treatment of fibromyalgia was recently published [Arnold et al, 2006]. The trial reported significantly greater improvements with gabapentin (1200 – 2400 mg/d) than with placebo at endpoint; results were not inconsistent with those reported during pregabalin trials. However, given the size of the trial and the lack of any comparative evidence, there is probably insufficient evidence to draw any conclusion regarding the relative efficacy or safety of pregabalin or gabapentin for the treatment of fibromyalgia; more clinical evidence is available for pregabalin.

The P&T Committee agreed that pregabalin should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria) who have failed an adequate trial, been unable to tolerate, or for whom treatment with TCAs or cyclobenzaprine is contraindicated or clinically inappropriate (e.g., due to potential cardiac effects).

Duloxetine for Fibromyalgia – Although duloxetine is not FDA-approved for fibromyalgia, its use is supported by two placebo-controlled RCTs [Arnold et al, 2004; Arnold et al, 2005]. Results are not inconsistent with those reported during pregabalin trials, although there is probably insufficient evidence to draw any conclusion regarding relative efficacy or safety of the two agents for the treatment of fibromyalgia. Duloxetine's therapeutic effect in fibromyalgia is most likely due to a distinctly different mechanism than pregabalin and likely includes effects on comorbid conditions, such as depression and anxiety, as well as pain.

Current MN criteria for duloxetine allow for its use in patients who have failed an adequate trial, been unable to tolerate, or for whom treatment with at least one medication from at least two of the following four drug classes is contraindicated or clinically inappropriate: TCAs (e.g., amitriptyline); tricyclic muscle relaxants (cyclobenzaprine); SSRIs (e.g., fluoxetine); or opioids (e.g., tramadol). The P&T Committee agreed that, given the evidence for pregabalin and its recent FDA approval for this indication, duloxetine MN criteria should be changed accordingly. At the same time, the P&T Committee agreed that SSRIs and opioids should be dropped from MN criteria due to inconsistent clinical evidence supporting the use of SSRIs for fibromyalgia and the overly broad definition of opioids. The P&T Committee agreed that duloxetine should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria), who have failed an adequate trial, been

unable to tolerate, or for whom treatment with both TCAs or cyclobenzaprine AND pregabalin is contraindicated or clinically inappropriate.

F. Administration Action – Modification of Mecasermin PA Criteria – The PEC reported an administrative change to mecasermin PA criteria to remove references to mecasermin rinfabate (Iplex) following its withdrawal from the market due to the outcome of litigation. Increlex is now the only mecasermin product on the market. The manufacturer of Iplex will continue to develop it for non-short stature indications (e.g., myotonic muscular dystrophy, Lou Gehrig's disease, HIV-associated adipose redistribution syndrome, and retinopathy of prematurity), but it is likely to be some time before data are available.

G. Statin Budget Impact Analysis (BIA) Review – The P&T Committee reviewed the performance of the Antilipidemic-1 (LIP-1) budget impact model used to estimate the outcome of potential formulary scenarios. The review compared actual Military Health System (MHS) pharmaceutical expenditures to the predicted expenditures that were reported at the August 2006 P&T meeting for the LIP-1 drug class. Data were collected for two quarters following UF implementation in January 2007. The results were compared directly and reported as a percent deviation from the actual values.

Study results showed that the model performed adequately during the first two quarters following the implementation date. The largest departure from actual spending occurred at the military treatment facility (MTF) point of service primarily because of conservative assumptions made about the price of generic simvastatin. The analysis assumed modest reductions in price for simvastatin after generic entry but in actuality the price fell more rapidly then what was predicted. More data will be collected in the future to determine if model performance is sustained. Furthermore, several findings from this review will be incorporated into future budget impact models to improve the validity and reliability of model results.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on four new drugs which were approved by the FDA (see Appendix B). The P&T Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) for budesonide/formoterol (Symbicort) oral inhaler, based on existing QLs for other oral inhalation products and recommendations for use in product labeling.

COMMITTEE ACTION: QUANTITY LIMITS

The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

1) Aliskiren Relative Clinical Effectiveness – The DoD P&T Committee evaluated the clinical effectiveness of aliskiren, a new direct renin inhibitor. Aliskiren is classified as a renin angiotensin antihypertensive agent (RAA). The RAA drug

class was defined at the May 2007 DoD P&T Committee meeting, and includes the following categories of drugs:

- *Angiotensin Receptor Blockers (ARBs) - May 2007*
  - **UF/Basic Core Formulary (BCF)**: telmisartan (Micardis), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT)
  - **UF:** candesartan (Atacand), candesartan HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar)
  - **Non-Formulary**: eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), valsartan (Diovan), valsartan/HCTZ (Diovan HCT)
- *ARB/Calcium Channel Blockers – February 2006*
  - **UF/BCF:** benazepril/amlodipine (Lotrel, generics)
  - **Non-Formulary:** enalapril/felodipine (Lexxel), trandolapril/verapamil sustained release (Tarka)
- *Angiotensin Converting Enzyme (ACE) inhibitors – August 2005*
  - **UF/BCF:** lisinopril (Prinivil, Zestril, generics), lisinopril/HCTZ (Prinzide, Zestoretic, generics), and captopril (Capoten, generics)
  - **UF**: captopril/HCTZ (Capozide, generics), benazepril (Lotensin, generics), benazepril/HCTZ (Lotensin HCT, generics), enalapril (Vasotec, generics), enalapril/HCTZ (Vasoretic, generics), fosinopril (Monopril, generics), fosinopril/HCTZ (Monopril-HCT, generics), trandolapril (Mavik)
  - **Non-Formulary:** ramipril (Altace), quinapril (Accupril, generics), quinapril/HCTZ (Accuretic, generics), perindopril (Aceon), moexipril (Univasc, generics), moexipril/HCTZ (Uniretic, generics)

Pharmacology – Aliskiren is the first direct oral renin inhibitor marketed in the U.S. It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. The correlation between decreased plasma renin activity and improved clinical outcomes is unclear.

Efficacy Measures – Clinical trials evaluating efficacy of aliskiren (typically 8 weeks in duration) have only assessed blood pressure (BP) reductions as the primary endpoint. Clinical trials have included patients with mild to moderate hypertension (mean diastolic BP 95-110 mm Hg); patients with severe hypertension have been excluded from clinical trials, along with patients with severe cardiac disease or renal impairment.

Efficacy Results – A pooled analysis from eight randomized trials reported mean reductions in seated BP with aliskiren 150 mg of 8.7-12/7.8-10.2 mm Hg and with aliskiren 300 mg of 14.1-15.9/10.3-12.3 mm Hg (not placebo adjusted). Aliskiren has been compared to ARBs (irbesartan, losartan and valsartan), diuretics (HCTZ) and the ACE inhibitor ramipril, as monotherapy and as combination therapy.

Overall, BP reductions with aliskiren were dose-related and were similar to that seen with the other drugs used as monotherapy; combination therapy produced additional BP reductions.

Outcomes Trials – Outcomes trials are currently underway, but results are not yet available. Trials are evaluating efficacy and safety of aliskiren in heart failure, post-myocardial infarction, diabetic nephropathy, left ventricular hypertrophy, diabetes, and metabolic syndrome. Initial results are expected in November 2007 for a study evaluating change in urinary albumin to creatinine ratio with aliskiren compared to losartan plus placebo (AVOID study) and a study evaluating reductions in brain natiuretic peptide in patients with hypertension and stable heart failure (ALOFT).

Safety – Available clinical data suggest that aliskiren most closely resembles an ARB in terms of adverse effects. Angioedema and hyperkalemia have been reported. Pooled data from clinical trials reported a discontinuation rate due to adverse effects of 2.2% with aliskiren vs. 3.5% with placebo. Dose-related diarrhea is the most common adverse effect. Clinically, aliskiren does not appear to inhibit or induce cytochrome P450 (CYP450) enzymes. Drug interactions have been reported with furosemide (decreased diuretic blood concentrations), and ketoconazole (increased aliskiren concentrations).

Place in Therapy – The exact place in therapy for aliskiren for treating hypertension is unknown at this time. Although aliskiren is indicated for use as monotherapy, it will likely be used as adjunctive therapy with other antihypertensive drugs (e.g., ACE inhibitors, ARBs, diuretics). A potential role for aliskiren would be in patients requiring double blockade of the renin-angiotensin aldosterone system; clinical trials with an ACE inhibitor plus an ARB in both heart failure and in patients with diabetic renal disease have suggested benefit; aliskiren could potentially be substituted for the ACE inhibitor in these settings.

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

a) Aliskiren is a new antihypertensive agent with a novel mechanism of action as a direct renin inhibitor.

b) Aliskiren's BP lowering effects are similar to those achieved with other antihypertensives, but it does not show improved efficacy compared to other classes of antihypertensive agents.

c) Combination therapy of aliskiren with ACE inhibitors, diuretics and ARBs has shown additive BP lowering effects compared to monotherapy with other antihypertensive agents.

d) Several other safe, once-daily, less costly antihypertensive drugs are available that have proven clinical outcomes (e.g., ACE inhibitors, ARBs, diuretics).

e) The long-term adverse event profile of aliskiren is unknown; diarrhea is the most commonly reported adverse event and the discontinuation rate is similar to placebo.

f) Clinical outcomes of aliskiren are unknown. Trials are underway, with initial results anticipated in November 2007.

The P&T Committee voted (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical conclusions stated above. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

2) *Aliskiren Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of aliskiren in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the ARBs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of aliskiren. The cost effectiveness of aliskiren was evaluated relative to ARBs, which were recently evaluated at the May 2007 DoD P&T Committee meeting.

The results of the CMA showed that the projected weighted average daily cost of aliskiren was higher than the weighted average daily cost of the ARBs designated as formulary on the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

> Although aliskiren was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren non-formulary at this time given its novel mechanism of action and the anticipated availability of clinical outcomes data that would enable the P&T Committee to more definitively asses its value relative to other antihypertensives.

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

3) *Aliskiren UF Recommendation*

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of aliskiren, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be designated as formulary on the UF.

4) *Aliskiren MN Criteria* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *Aliskiren Implementation Plan* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

1) *Fluticasone Furoate Relative Clinical Effectiveness* – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005. Nasal corticosteroids on the UF include fluticasone propionate (Flonase, generics),

mometasone furoate (Nasonex) and flunisolide (Nasarel). Fluticasone propionate is classified as the BCF agent. The non-formulary nasal corticosteroid agents are beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA).

Pharmacology – Fluticasone furoate is a new nasal corticosteroid marketed by GlaxoSmithKline, the manufacturer of fluticasone propionate, which has been available in a generic formulation since February 2006. Veramyst is structurally different from Flonase in that fluticasone propionate ester has been replaced with fluticasone furoate ester. Fluticasone furoate is active as the intact molecule and is not a prodrug or alternative salt of fluticasone. The structural change is responsible for higher glucocorticoid receptor binding affinity. However, *in vitro* claims of enhanced receptor binding have not translated into improved clinical effectiveness.

FDA-Approved Indications – Both fluticasone furoate and fluticasone propionate are FDA-approved for treating symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children. Fluticasone furoate and mometasone are approved for use in children down to the age of 2 years, compared to 4 years with Flonase. In contrast to mometasone furoate, Veramyst is not currently approved for treatment of nasal polyps.

Efficacy – Efficacy assessment was based on the total nasal symptom score (TNSS), which was calculated based on the sum of a patient's score for four individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, nasal itching). This was often reported as a reflective total nasal symptom score (rTNSS), which averages previous daytime and nighttime TNSSs over a certain time period.

Head-to-Head Trial-- There is insufficient evidence to determine if there are clinically relevant differences between fluticasone furoate and fluticasone propionate. One head-to-head trial in patients older than 12 years of age with SAR showed that fluticasone furoate was not inferior to fluticasone propionate in terms of changes from baseline in TNSS.

Placebo-Controlled Trials – FDA-approval of fluticasone furoate was based on six placebo-controlled trials.

a) In the trials enrolling adults with SAR (three studies) or PAR (one study), fluticasone furoate 110 mcg/day showed statistically significant improvement in rTNSS when compared to placebo.

b) In one study in children younger than 12 years with PAR, fluticasone furoate 55 mcg showed a statistically significant improvement in nasal symptom scores (rTNSS) compared to placebo; however there was no difference between placebo and Veramyst 110 mcg.

c) In the one pediatric study in patients with SAR, fluticasone furoate 110 mcg but not 55 mcg showed a statistically significant improvement in rTNSS compared to placebo.

Efficacy in Treating Ocular Symptoms – Nasal corticosteroids have not shown efficacy at reducing ocular symptoms of AR, in contrast to benefits seen with oral

antihistamines. With fluticasone furoate, although some improvements were noted in individual ocular symptoms evaluated as secondary endpoints (e.g., eye watering/tearing, eye itching/burning, and eye redness), there was no difference from placebo when reflective total ocular symptom score was evaluated as a primary endpoint.

Safety – The adverse event profile of fluticasone furoate is similar to other nasal corticosteroids. Common adverse events reported with fluticasone furoate included headache, epistaxis, and nasal ulceration. Administration of fluticasone furoate with ritonavir, a potent CYP3A4 inhibitor, is not recommended, due to the potential for increased systemic effects of fluticasone furoate.

Delivery Device – The Committee also evaluated differences in the delivery device, ease of administration, and particle size of fluticasone furoate compared to other nasal corticosteroids, but did not find a unique advantage or disadvantage relative to fluticasone propionate or mometasone furoate.

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

> Fluticasone furoate has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other nasal corticosteroids included on the UF.

The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Fluticasone Furoate Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of fluticasone furoate in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   A CMA was employed to evaluate the cost effectiveness of fluticasone furoate relative to the UF nasal corticosteroids. The results of the CMA showed that the projected weighted average daily cost of fluticasone furoate was significantly higher than weighted average daily cost of the UF nasal corticosteroids.

   Cost Effectiveness Conclusion – The P&T Committee concluded that:

   > Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

   The P&T Committee voted (12 for, 0 opposed, 1 abstained, 4 absent) to accept the cost effectiveness conclusion stated above

3) *Fluticasone Furoate UF Recommendation*

   Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF.

4) *Fluticasone Furoate MN Criteria* – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended maintaining the medical necessity criteria previously established for the nasal corticosteroid class. The following general MN criteria will be applied for fluticasone furoate:

   1) The use of formulary alternatives is contraindicated.

   2) The patient has experienced significant adverse effects from formulary alternatives.

   3) Formulary alternatives have resulted in therapeutic failure.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Fluticasone Furoate Implementation Plan* – There have been approximately 650 prescriptions for fluticasone furoate in the MHS, all in the TRICARE Retail Pharmacy Network (TRRx), since market introduction. The Committee discussed the merits of a 60-day implementation period. Additionally, Committee members directed that if operationally feasible, the $22 co-pay should start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current Veramyst users.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. If determined to be operationally feasible, the $22 co-pay would start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current Veramyst users.

6) *Fluticasone Furoate QL* – The P&T Committee evaluated the need for QLs for fluticasone furoate. QLs are in effect for other nasal corticosteroids. Based on both adults and pediatric dosing in manufacturer labeling for fluticasone furoate, the number of doses in an inhaler (120 metered doses), and QLs for other nasal corticosteroids, the P&T Committee recommended QLs for fluticasone furoate.

   COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for fluticasone furoate in the TRRx for 1 inhaler device per 30 days and in the TMOP for 3 inhaler devices per 90 days.

6. DRUG CLASS REVIEW – NEWER ANTIHISTAMINES (NAs)

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents (listed in order of FDA approval): loratadine (Claritin, generics), acrivastine/pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. Loratadine (Claritin, generics), cetirizine (Zyrtec), and desloratadine (Clarinex) are FDA-

indicated for the treatment of SAR, PAR, and chronic idiopathic urticaria (CIU). Fexofenadine is indicated for the treatment of SAR and CIU. Acrivastine/ pseudo-ephedrine is only indicated for the treatment of SAR.

All of the NAs are classified as inverse agonists of the H_1-receptor; they act to stabilize the H_1-receptor in its inactive conformation. Histamine is the main inflammatory mediator involved in the development of the majority of the symptoms seen in conditions treated with NAs.

As of June 2007, about three million MHS prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 . Across the MHS, cetirizine is the most commonly prescribed NA, followed by fexofenadine then loratadine. Usage of desloratadine and pseudoephedrine combination products is low and stable, while usage of acrivastine/pseudoephedrine is rare.

The brand-only agents are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Brand-name cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for the newly FDA approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007. Levocetirizine was not included in the current review; it will be addressed at a future meeting.

A. NAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the NAs currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Allergic rhinitis (AR) affects an estimated 20 to 40 million people in the United States. Multiple symptoms are associated with AR, including sneezing, itching, nasal congestion and rhinorrhea. These symptoms arise from different allergens comprised of pollens, molds, dust mites, and animal dander. Although AR is a term collectively used to define these symptoms, there are two different classifications, SAR or intermittent AR, and PAR or persistent AR.

SAR or “hay fever” is the rapid and reproducible onset and offset of symptoms in association with pollen exposure. PAR is more difficult to diagnose, because the symptoms of PAR overlap with symptoms of chronic sinusitis, upper respiratory infections and vasomotor rhinitis. Patients with PAR are affected with symptoms at least 9 months of a year. It is estimated that about 20% of the patients with AR suffer

from SAR, 40% from PAR, and 40% with both SAR and PAR (PAR with seasonal exacerbations).

CIU is defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks, with no obvious cause. CIU has not been the subject of detailed epidemiological studies. Published figures for frequency are confounded by uncertainty of the diagnosis, since the term "chronic idiopathic urticaria" is often taken to encompass physical urticarias. It has been estimated that about 0.1% of the population suffers from CIU, and 50% of these patients have symptoms for more than a year. Up to 20% of patients with symptoms greater than one year go on to have symptoms for 20 years or more. CIU is a major affliction causing serious disability.

1) *Efficacy*

The relative clinical effectiveness evaluation was based upon an evidence-based review of the clinical literature found in PubMed, Cochrane Library, National Guidelines Clearinghouse and reference lists of systematic review articles published through June 2007. In particular, this evaluation relied heavily upon the following sources: the Allergic Rhinitis and Its Impact on Asthma (ARIA) 2001 Guidelines and the draft 2007 update; the Agency for Healthcare Research and Quality 2002 Evidence and Technology Report/World Health Organization: Rhinitis; the European Dermatology Forum 2004 Consensus Statement: Urticaria; and the Oregon Drug Effectiveness Review Project (DERP) 2004 and 2006 Drug Class Review.

a) Seasonal Allergic Rhinitis

Adults

The Committee concluded that for the treatment of SAR in adults that there was insufficient evidence to suggest clinically significant differences in efficacy between fexofenadine, loratadine and cetirizine or desloratadine and fexofenadine. There is insufficient evidence to compare acrivastine/ pseudoephedrine to the other agents in the treatment of SAR.

Five head-to-head comparative trials assessed the efficacy of various NAs in the treatment of SAR in adults. The trials varied in country, season, and baseline characteristics of patients. These trials demonstrated no statistically significant difference between agents in total symptom score (TSS) change from baseline between cetirizine versus loratadine, cetirizine versus fexofenadine, or loratadine versus fexofenadine. The trials were too heterogeneous for meta-analysis. A recent head-to-head trial [Berger 2006] compared the efficacy of desloratadine and fexofenadine to placebo in patients with SAR. Results showed that both agents provided comparable efficacy, and were more effective than placebo. In the trial, subjects were randomized to desloratadine 5 mg, fexofenadine 180 mg once daily, or placebo. Mean daytime instantaneous TSS was significantly reduced from baseline by 28% with desloratadine, $p = 0.006$ and by 27% with fexofenadine, $p = 0.024$ versus placebo. The between agent mean TSS reduction was not statistically different ($p = 0.491$).

Children

There is insufficient evidence to suggest any clinical significant differences in efficacy in the treatment of SAR in children ≤ 12 years. There were no head-to-head comparative trials identified for children with SAR. Placebo and active controlled trials demonstrated that cetirizine, fexofenadine, and loratadine were more effective than placebo.

b) Perennial Allergic Rhinitis

Adults

The committee concluded that for the treatment of PAR in adults there is insufficient evidence to suggest clinically significant differences between the agents. Desloratadine has shown efficacy in the treatment of PAR in adults in a placebo-controlled trial, while loratadine has shown efficacy compared to placebo in an active-controlled trial that also included the older antihistamine clemastine. There were no head-to-head trials of sufficient quality identified for adults with PAR.

Children

There is insufficient evidence to suggest any clinically significant differences in efficacy in the treatment of PAR in children ≤ 12 years. There was one head-to-head comparative trial for loratadine versus cetirizine. The parent assessment results of this 4-week trial in 80 children, ages 2 to 6, showed cetirizine to be more effective than loratadine ($p < 0.001$) in relieving nasal symptoms associated with PAR. However, the global evaluation score by investigator showed no statistically significant difference. Placebo- and active-controlled trials for cetirizine and a placebo-controlled trial for loratadine showed the agents to be more effective than placebo in the treatment of PAR.

c) Chronic Idiopathic Urticaria

Adults

For CIU, the P&T Committee concluded that limited evidence suggests loratadine may be more effective than cetirizine and that cetirizine may be more effective than fexofenadine in adults.

Two fair quality head-to-head trials in adults with CIU were identified. One trial reported that loratadine 10 mg QD was more effective ($p<0.01$) in reducing TSS than cetirizine 10 mg QD or placebo [loratadine -81%, cetirizine -69%, placebo -55%]. There was no statistically significant difference in response rate between the two active agents [loratadine 63% vs. Cetirizine 45%, placebo 13%]. The other comparative trial reported that cetirizine 10 mg QD was more effective (p-value not reported) than fexofenadine 180 mg QD in symptom-free patients [cetirizine 51.9% vs. Fexofenadine 4.4%].

Children

Only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

2) *Safety / Tolerability*

As a class, the NAs are safe and well tolerated. There are few drug-drug interactions and clinical trial withdrawal rates are low (2 to 3%). The drugs can be used extensively in special populations.

Adverse Effects – While adverse effects with NAs occurred at a rate between 21 to 51% in clinical trials included in the 2006 DERP review, they tended to be minor, similar to placebo, and associated with a low discontinuation rate (2 to 3%). Minor adverse effects included stomach pain, lightheadedness, headache, and nausea.

Sedation – The NAs generally cause less drowsiness and sedation than older antihistamines. Cetirizine has been shown to cause more sedation than fexofenadine and loratadine. Loratadine and desloratadine, while causing minimal sedation at recommended dosages, have shown to cause significant sedation at higher doses. Fexofenadine has not shown sedation even in doses as high as 360 mg.

Cardiac arrhythmias – Cardiac toxicity has been a concern with NAs in the past, but does not appear to be a major issue with currently marketed products. Astemizole (Hismanal) and terfenadine (Seldane), two of the first newer antihistamines, were removed from the market because of their potential to cause prolonged QTc and torsade de pointes. However, newer second generation antihistamines have undergone extensive testing regarding their propensity to cause cardiac arrhythmias. Juniper et al (2005) reviewed these studies and concluded that cetirizine, fexofenadine and loratadine appear to have little potential to cause arrhythmias.

Pseudoephedrine-Containing Products – Combination products with pseudoephedrine can cause central nervous system stimulation, dizziness, weakness and insomnia. Pseudoephedrine has also been noted to cause palpitations as well as anxiety. Combination products containing pseudoephedrine are contraindicated in patients with narrow angle glaucoma, urinary retention, and with monoamine oxidase inhibitors (MAOIs). They should be used with *caution* in patients with hypertension, diabetes mellitus, ischemic heart disease, increased in ocular pressure, hyperthyroidism, renal impairment, and prostatic hypertrophy, and with *extreme* caution in patients with severe hypertension and/or severe coronary artery disease.

Use in Special Populations

- *Renal Failure* – All the NAs except acrivastine/pseudoephedrine have alternative dosing recommendations for patients with moderate to severe renal failure. Acrivastine/pseudoephedrine is not recommended in patients with a creatinine clearance less than or equal to 48 mL per minute.
- *Hepatic Failure* – Cetirizine, desloratadine, and loratadine have alternative dosing recommendations for patients with hepatic failure. Because

fexofenadine is metabolized to a very small extent, dosing changes in patients with hepatic failure is not necessary. The manufacturers of acrivastine/ pseudoephedrine have not made recommendations for alternative dosing of patients with hepatic failure.

- *Geriatrics* – There is insufficient data for manufacturers to make recommendations in populations greater than 70 years of age.
- *Pediatrics* – All the drugs, except acrivastine/pseudoephedrine and pseudoephedrine combination products, have indications for pediatric patients. Cetirizine, fexofenadine, and desloratadine have dosing recommendations for patients down to age 6 months. Loratadine has indications for patients to age 2 years and older.
- *Pregnancy and Lactation* – Acrivastine/pseudoephedrine, cetirizine and loratadine are FDA pregnancy category B. Although evidence from a randomized, controlled trial is not available, a cohort study of Israeli women showed no increase in major abnormalities of children born to women exposed to loratadine (RR 0.77; 95% CI 0.27 to 2.19) when compared to a no treatment control group. Secondary measures, including rate of still births, preterm deliveries and median birth weight, were similar between cohort groups. Desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

  The manufacturer states that loratadine is compatible with breast-feeding. The manufacturers of other agents state that infant risk cannot be ruled out.

Drug Interactions

Drug interactions with ketoconazole and/or erythromycin have been reported with loratadine, desloratadine, and fexofenadine. However, despite the increased blood levels, there were no changes in QT interval, clinical condition, lab tests, or reported adverse events; dosage changes are not considered to be necessary. Antacids appear to reduce the area under the curve of fexofenadine by ~43%. Acrivastine/ pseudoephedrine and pseudoephedrine combination products can interact with antihypertensive drugs and reduce their antihypertensive effect. They should not be given within 14 days of a MAOI.

3) *Other Factors*

The NAs do not appear to differ significantly with regard to the availability of additional formulations, with the exception of acrivastine/pseudoephedrine. All the single agent products have multiple alternate dosage formulations (oral dissolving tablets, rapid dissolving tablets, solutions or suspensions) and combination products containing pseudoephedrine.

4) *Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) Based on randomized placebo-controlled trials, cetirizine, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of SAR, PAR and CIU. Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR, and CIU. Acrivastine/pseudoephedrine is more efficacious than placebo for the symptomatic relief of SAR.

b) Based on six comparative trials in adults with SAR, there is insufficient evidence to suggest that there are clinically significant differences between cetirizine, fexofenadine, and loratadine, or desloratadine and fexofenadine. There is insufficient evidence to compare any of the agents in children less than 12 years old with this condition.

c) For the treatment of PAR in adults, there is insufficient evidence to suggest clinically significant differences between the agents. In children 2 to 6 years old, limited evidence based on one fair/poor quality comparative trial suggests that cetirizine may be more efficacious than loratadine with PAR.

d) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

e) The NAs appear to have similar adverse effect profiles and to result in similar low rates of discontinuation due to adverse events in clinical trials. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions.

f) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

g) All the parent products have multiple dosage forms and a pseudoephedrine-containing combination product.

h) It is likely that at one NA is sufficient for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

i) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. NAs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the NAs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the NAs differed in regards to efficacy, safety, tolerability, or

clinical outcomes data. As a result, CMAs were performed to compare the relative cost effectiveness of the single agent NAs and the pseudoephedrine combinations. The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the NA CMAs showed that desloratadine and desloratadine/pseudoephedrine were not cost effective relative to the other agents in the newer antihistamine class. All other medications in the class were determined to be cost effective relative to their comparators.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of NAs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Desloratadine and desloratadine/pseudoephedrine were not cost effective relative to other comparable agents in the newer antihistamine class.
2) The UF scenario that designated desloratadine and desloratadine/pseudoephedrine as non-formulary under the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusion stated above.

C. NAs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that:

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/pseudoephedrine, and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available over-the-counter, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

D. NAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for desloratadine and desloratadine/pseudo-ephedrine:

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that acrivastine/pseudoephedrine, like other NA combination products with pseudoephedrine, is not indicated in children younger than 12 years of age.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. NAs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA

MTFs will not be allowed to have desloratadine and desloratadine/pseudoephedrine on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary NA agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. NAs – BCF Review and Recommendations – The P&T Committee considered the BCF status of the NA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single-ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. The P&T Committee noted that loratadine is the most cost effective NA in the MTFs, at approximately 1/12 the cost of the next most competitively priced agent.

7. DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LMs. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available and was not included in the review.

Currently montelukast is the only BCF LM agent. None are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

A. LMs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the LMs marketed in the U.S. By considering information regarding their safety, effectiveness and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

1) *FDA-approved indications*

a) Asthma

Montelukast, zafirlukast and zileuton are all indicated for the treatment of asthma in adults and children. Montelukast is approved in children as young as one year of age, zafirlukast is indicated in children down to age of six years, and zileuton is approved for use in children aged 12 years and older. The LMs are most often used as adjunctive therapy to first-line asthma therapies including inhaled corticosteroids (ICSs) and long-acting beta agonists (LABAs).

b) SAR and PAR

Montelukast is the only LM with indications other than asthma; it is FDA-approved for treating allergic rhinitis in adults and children. For SAR, montelukast is approved down to the age of two years, and for PAR down to the age of six months.

c) Exercise-Induced Bronchoconstriction (EIB)

In April 2007, montelukast received approval for use in EIB in patients older than 15 years of age.

2) Efficacy

a) Asthma

i) National guidelines – The National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education Prevention Program (NAEPP)

guidelines state that LMs are not first-line therapy. For all age groups, ICSs are considered first-line. In adolescents older than 12 years and adults, LABAs are preferred over LMs for adjunctive therapy; in this age group zileuton is an alternative, but not preferred therapy due to limited efficacy data and requirements for liver function test (LFT) monitoring. For younger children, LMs are an alternative based on the convenience of delivery device (oral administration vs. Nebulizer or oral inhaler) and safety data, rather than efficacy data.

ii) Meta-Analyses and Systematic Reviews – Three meta-analyses evaluated efficacy of the LMs compared with other asthma controller therapies.

- Sin et al (JAMA 2004) found that LMs were less effective than ICSs in reducing asthma exacerbations and improving forced expiratory volume in 1 second (FEV1) (RR 1.72; 95% CI 1.28-2.31).
- ICSs were also preferred in a Cochrane review (Ducharme, DiSilva) where patients taking LMs versus those taking ICSs were approximately 60%-70% more likely to have an asthma exacerbation (RR 1.65; 95% CI 1.36-2.0). Other endpoints such as FEV1 improvements, withdrawal rates from therapy due to poor symptom control, and asthma symptoms scores were consistently more favorable with ICSs.
- A second Cochrane review (Ducharme, Kakauma) that compared the combination of LMs to ICS versus ICS alone demonstrated minimal differences in combination therapy versus monotherapy (e.g., decreased need for albuterol by only one puff per week and no change in steroid dose vs. using the ICS alone). The combination of LABA plus ICS was superior in preventing asthma exacerbations requiring oral steroids than the combination of LM plus ICS.

iii) Clinical Trials – There are no head–to-head clinical trials evaluating the LMs for asthma. Results of placebo controlled trials or trials using ICS as an active comparator show that all three LMs produced statistically significant changes in FEV1, peak expiratory flow, and asthma symptoms score, compared to placebo. Indirect comparisons of placebo-controlled trials with similar study design using montelukast and zafirlukast suggest similar effects on asthma control, based on increases in FEV1 and as-needed beta agonist use. Fewer studies are available with zileuton.

iv) Steroid-Sparing Effects –Whether the LMs allow a reduction in ICS dose is controversial. The product labeling for montelukast states that a lower dose of ICS than previously used was able to control asthma symptoms when the LM was added on to ICS in one study in 226 patients. The Ducharme/Kakauma Cochrane analysis found no effect on steroid dose when a LM was added on to ICS. There is insufficient evidence to determine the steroid sparing effects of zafirlukast and zileuton. NHLBI/ NAEPP guidelines caution that the steroid sparing effects of the LMs are inconclusive, and that patients cannot be entirely weaned from the ICS.

b) *Exercise Induced Bronchoconstriction*

i) *National Guidelines* – NHLBI/NAEPP guidelines for EIB consider albuterol as the drug of choice, as albuterol prevents EIB in more than 80% of patients and is backed by good quality (Level A) evidence. Similar efficacy rates are seen with the LABAs (also considered Level A evidence); however, caution is required as tolerance develops with chronic use. In contrast, montelukast attenuates EIB in 50% of patients and is supported by Level B evidence. The guidelines stress that EIB is frequently a marker of inadequate asthma management, and that prevention and improved asthma control are recommended.

ii) *Clinical Trials* – Montelukast received FDA approval for EIB in patients older than 15 years in April 07 based on a placebo controlled trial showing a statistically significant benefit 2 hours after dosing. Montelukast has an onset of action of 1-2 hours, and a duration of action lasting up to 24 hours. There are no head-to-head trials comparing montelukast with albuterol. Two comparative trials with montelukast and salmeterol (Serevent) showed similar efficacy at preventing EIB within one hour prior to exercise. One study has evaluated efficacy of zileuton for EIB, but it is not approved by the FDA for this use.

c) *Allergic Rhinitis*

i) *Efficacy Measures* - Meta-analyses and clinical trials evaluating treatment for AR most frequently used two efficacy measures; variations of the rhinitis symptom score where the severity of nasal symptoms of congestion, itching, rhinorrhea are assessed, and the rhinoconjunctivitis-specific quality of life (RQLQ).

ii) *National Guidelines* – A preview of the updated Allergic Rhinitis in Asthma (ARIA) guidelines from the World Health Organization lists NAs or nasal corticosteroids (NCS) as first-line therapy for mild AR; the combination of a NA and NCS for moderate AR; and the combination of NA and NCS plus a LM for severe AR.

iii) *Meta-Analyses and Systematic Reviews* - Two meta-analyses have evaluated efficacy of the LMs vs. NCS and NAs for SAR; one by Wilson et al (2004) and the other by Rodrigo et al (2006).

- *LM vs. Placebo* – The Wilson meta-analysis included eight RCTs (one with zafirlukast; 7 with montelukast; over 3,900 patients) comparing a LM either alone or in combination with NAs or NCS vs. placebo or other treatments. The LMs significantly improved the nasal symptom score 5% more than placebo (95% CI 3-7%). This was of questionable clinical significance, as the authors used a 10% change as designating a minimally important result. There is no one recognized minimally important change in nasal score.

  The four studies where RQLQ was evaluated found that the LM significantly improved RQLQ by 0.3 units compared with placebo

(95% CI 0.24 to 0.36). A minimally important change in RQLQ is accepted to be a change of at least 0.57 units.

- *LM vs. NAs* – The treatment efficacy of LMs vs. NAs was compared in both the Wilson (4 RCTs) and Rodrigo (5 RCTs) meta-analyses. The trials included all compared montelukast with loratadine. In the Wilson analysis, loratadine improved nasal symptom score 2% more than montelukast, but the results were not statistically significant (95% CI 0% to 4%). Treatment with loratadine significantly improved RQLQ by 0.11 units more than montelukast (95% CI 0.04 to 0.18 units). The Rodrigo meta-analysis found no statistically significant difference between montelukast and loratadine in nasal symptom score or RQLQ; additionally, when individual eye symptoms were scored, there was no significant difference between montelukast and loratadine.
- *LM vs. NCS* – In the Wilson meta-analysis, montelukast was compared with fluticasone (3 RCTs), mometasone (1 RCT), budesonide (1 RCT), and zafirlukast was compared with beclomethasone (1 RCT). NCS improved nasal symptom score 12% more than the LM (95% CI 5% to 18%); RQLQ was not assessed.
- *LM plus NA vs. NCS* – The Rodrigo meta-analysis evaluated the combination of LM with a NA vs. NCS. Overall there were only minimal differences noted, although there was a trend toward superiority of the NCS.

iv) PAR – There are no meta-analyses evaluating LM efficacy for PAR. Montelukast is the only LM approved for PAR, which was supported by one placebo-controlled trial in over 1,900 patients that showed statistically significant improvements in daytime and nighttime symptom scores, RQLQ scores, and provider and patient global assessment.

In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

v) Pediatric Issues

- *FDA Labeling* – Although montelukast is approved for patients as young as 6 months with PAR, and as young as 2 years with SAR, the product labeling states that efficacy data is extrapolated from studies with adolescents older than 15 years with AR.
- *Clinical Trials* – Two small placebo-controlled studies evaluated montelukast with cetirizine in Taiwanese children ranging in age from 2-6 years and 6-12 years with PAR. Cetirizine was statistically

significantly superior to montelukast in improving total nasal symptoms and the individual symptom of nasal congestion.

- *National Guidelines* – The ARIA guidelines for children recommend following the same principles as adults. They acknowledge that NCS are the most effective treatment of pediatric AR, but recognize that long-term safety remains controversial for growth suppression and hypothalamic-pituitary axis suppression.
- *Other Treatments* – Other treatments for AR are approved for use in children as young as 6 months (cetirizine, fexofenadine, and desloratadine), two years (loratadine and mometasone), and 4 years (fluticasone propionate).

d) Off-Label Uses

The Committee reviewed several off-label uses for the LMs; most of these lack sufficient data to prove safe and efficacious use at this time. Treatment of nasal polyps and treatment of reactive airways disease after acute respiratory syncytial virus illness in children appear to have sufficient published evidence to prove safe and clinically effective.

3) *Safety and Tolerability*

a) Serious Adverse Effects

i) Churg-Strauss Syndrome – Case reports of montelukast and zafirlukast causing systemic eosinophilic vasculitis in patients with asthma and AR are available. However, it is uncertain whether this is a direct effect of the LM or due to concomitant withdrawal of corticosteroids. There is insufficient evidence to determine whether one LM is more likely than another to cause this syndrome.

ii) Hepatotoxicity

- *Montelukast* – The product labeling states there are rare reports of hepatic injury without increases in LFTs. The incidence of in aspartate aminotransferase (AST) elevations is 1.7% with montelukast vs. 1.2% with placebo.
- *Zafirlukast* – Product labeling describes rare reports of hepatic failure, with resolution of symptoms and LFT elevations upon drug discontinuation; there is no requirement in labeling for LFT monitoring. According to the manufacturer, there have been eight published cases linking zafirlukast with hepatic failure, two of which required transplant. Information received in response to a Freedom of Information Act request to the FDA revealed 66 cases of hepatitis or liver failure and 23 deaths between 1997 and 2002. These cases were spontaneous reports, and a direct causality with zafirlukast has not been assessed.
- *Zileuton* – Use is contraindicated in patients with active hepatic disease of LFT elevations greater than 3 the upper limit of normal

(ULN). In clinical trials of over 5,000 patients, the incidence of AST elevations more than 3 times the ULN was 4.6% with zileuton. LFT monitoring is required at baseline, monthly for the initial three months of treatment, and every 2-3 months thereafter.

b) Minor Adverse Effects – Overall the LMs have a low incidence of minor adverse effects, with headache and gastrointestinal complaints reported most commonly. Pooled data from the product labeling suggests that there is no relevant difference between the LMs in minor adverse effects.

c) Drug-Drug Interactions – Montelukast has not been associated with clinically significant drug interactions. Zafirlukast and zileuton both can increase the prothrombin time when administered with warfarin (Coumadin). Zileuton can decrease theophylline metabolism, leading to increased theophylline concentrations; theophylline dosage reductions of 50% are required with concomitant use.

d) Special Populations – Montelukast is rated pregnancy category B, while both zafirlukast and zileuton are rated pregnancy category C. Dosage adjustments in renal impairment are not necessary with the LMs. Zileuton is contra-indicated for use in patients with active liver disease.

4) *Other Factors*

Montelukast is available in several dosage formulations (tablets, chewable tablet, and granules), and is dosed once daily. Zafirlukast requires BID dosing, while zileuton requires QID dosing.

5) *Therapeutic Interchangeability*

There is a low degree of therapeutic interchangeability between the three LMs. Montelukast has advantages in terms of multiple indications, multiple formulations, a more favorable safety profile, and FDA approval in the pediatric population.

6) *Clinical Coverage*

To meet the needs of MHS patients, one LM is required; however, it must have a favorable safety profile. For EIB, availability of montelukast, the only LM approved for this indication, is less urgent, due to efficacy and acceptance of albuterol and LABA.

7) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) For the treatment of asthma, NHLBI/NAEPP guidelines include LMs as alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than ICS, and are less effective when added on to LABA vs. use of a LABA with ICS. Addition of a LM to ICS provides modest benefit over use of the ICS as monotherapy.

b) In placebo-controlled trials for asthma, the three LMs montelukast, zafirlukast, and zileuton demonstrate clinical effectiveness in endpoints such as reduction in exacerbations, improvements in FEV1, asthma symptoms

scores and short acting beta-agonist use. There is insufficient evidence to determine whether one LM is more efficacious at controlling asthma symptoms than another.

c) Limited evidence suggests that LMs may permit a reduced inhaled steroid dose, or could be used in patients resistant or unable to tolerate ICS. The extent or clinical significance of this "steroid sparing" effect is uncertain.

d) Montelukast is the only LM that is FDA approved for the treatment of AR, and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of AR, but they fail to consistently show efficacy. There is no data to support the use of zileuton in AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR endpoints such as rhinitis symptoms scores and rhinoconjunctivitis quality of life scores; however, the treatment effect is modest. When compared to antihistamines, the LMs show relatively similar efficacy. NCSs are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine is modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

j) In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

k) In regard to safety and tolerability, zileuton has been associated with hepatotoxicity, requires LFT monitoring, and is contraindicated in patients with active liver disease. Zafirlukast has also been associated with hepatotoxicity including liver failure and death; however, this data is from spontaneously reported adverse events reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

l) In regard to other factors, montelukast has the advantage of a greater number of FDA approved indications, pediatric indications, less frequent dosing (once daily versus twice and four-times daily for zafirlukast and zileuton), and availability of alternative dosage formulations.

m) Overall, based on clinical issues alone, montelukast is preferred over zafirlukast, which in turn is preferred over zileuton.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical effectiveness conclusions stated above.

B. LMs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the LM agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation determined that there was enough evidence to show that the LM medications differed in regards to efficacy and safety in the treatment of asthma, AR, and EIB. Moreover, the clinical review concluded that the LMs have a role in the management of asthma and are gaining acceptance in the treatment of EIB. However, the use of LMs in AR remains controversial. As a result, the pharmacoeconomic analysis first compared the LMs in a CMA to gauge the cost effectiveness of the agents within the LM class. Once complete, the analysis then considered the cost effectiveness of LMs as compared to NAs and NCS in the treatment of AR. Each analysis compared the weighted average cost per day of treatment across all three points of service.

Results from the LM CMA showed that zafirlukast was the least costly agent in the class. In comparison, montelukast was more costly per day of treatment but also provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class. The least cost effective product was zileuton.

In the treatment of AR, the cost effectiveness analysis showed that NA agents and NCS agents were the most cost effective options for the treatment of AR. The LMs were less effective than the NCS and provided comparable efficacy to the NAs. However, the LMs were significantly more costly per day of treatment than either the NAs or the NCS agents. Hence, pervasive use of LMs as first-line therapy in AR should be discouraged to optimize treatment of AR in the MHS.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of a UF scenario that required a step therapy/PA program for use of LMs in allergic rhinitis (with no PA for other indications) was compared to a scenario with no PA required for use of LMs in any indication. The analysis was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to estimate the impact of enacting a step therapy/PA policy for AR in the LM class and to aid the Committee in determining which group of LMs best met the clinical needs of the majority of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Zafirlukast was the least costly agent in the class; montelukast was more costly relative to zafirlukast but provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class; zileuton was not cost effective relative to the other products.
2) LMs are not cost effective in the treatment of AR relative to antihistamines and NCS agents and should not be considered as first-line therapy in the treatment of AR.

3) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/PA required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

COMMITTEE ACTION: The DOD P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to accept the LM relative cost effectiveness analysis as presented by the PEC.

C. LMs – Step Therapy Consideration

For SAR and PAR (although montelukast is the only LM with this indication) the LMs are considered third-line agents after antihistamines and NCS. The Committee reviewed several programs utilized by civilian health plans to address use of the LMs for AR. Several plans allow unrestricted use of the LMs for asthma, but require PA for AR, primarily based on previous use of an antihistamine and/or NCS.

The Committee considered a step therapy/PA program where LMs would be allowed for MHS patients with asthma, but PA would be required for LM use in AR patients older than 5 years of age. Patients older than the age of 5 would require prior use of a NA and NCS, before LM use would be allowed.

COMMITTEE ACTION: Although the committee agreed that the LMs are not cost effective for AR, the Committee voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required.

D. LMs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF.

E. LMs – MN Criteria

Based on the clinical evaluation for zileuton, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for zileuton:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

3) Formulary agents have resulted in therapeutic failure.

4) Patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

With respect to criterion #4, the P&T Committee's primary concern was for asthma patients stabilized on zileuton, although this is likely to apply to very few patients considering the low usage of zileuton.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. LMs – UF Implementation Period

Approximately 145 beneficiaries (0.07% of those using agents in the LM class) will be affected by the UF decision. The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have zileuton on their local formularies. MTFs will be able to fill non-formulary requests for zileuton only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary LM agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. LMs – BCF Review and Recommendation

The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules).

8. DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

A. GSAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the GSA agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but

was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 1: Growth Stimulating Agents Available in the U.S.

Subclass	Generic Name	Brand Name	FDA Indication
Growth Hormone	Somatropin	Genotropin (Pfizer) Genotropin Miniquick	GHD, PWS, TS, SGA
		Humatrope (Eli Lilly)	GHD, TS, ISS, SHOX
		Nutropin (Genentech) Nutropin AQ	GHD, TS, CRI, ISS
		Norditropin (Novo Nordisk) Norditropin Nordiflex	GHD, Noonan's Syndrome
		Omnitrope (Sandoz)	GHD
		Saizen (Serono)	GHD
		Serostim (Serono)	AIDS/HIV wasting
		Tev-Tropin (Teva/Gate)	GHD (pediatric patients only)
		Zorbtive (Serono)	SBS
Insulin-like growth factor (IGF-1)	Mecasermin	Increlex (Tercica)*	IGFD

*A second mecasermin product, mecasermin rinfabate (Iplex; Insmed) has been withdrawn from the market due to patent litigation settlement; the manufacturer continues to develop the product for the treatment of non-growth related conditions.

GHD = Growth Hormone Deficiency; PWS = Prader-Willi Syndrome; TS = Turner Syndrome; SGA = Small for Gestational Age; ISS = Idiopathic Short Stature; SHOX = Short Stature Homeobox gene deficiency; CRI = Chronic Renal Insufficiency; SBS = Short Bowel Syndrome; IGFD = Insulin-like Growth Factor Deficiency

1) Background

a) Growth stimulant agents

i) Products

This class of drugs includes only two molecular entities, somatropin and mecasermin. There are multiple competing somatropin products. The majority of these are indicated for the treatment of GH deficiency (GHD), which is the most common use, although manufacturers are constantly researching additional FDA indications. Mecasermin is an orphan drug approved by the FDA in 2005 to treat severe primary insulin-like growth factor deficiency (IGFD), which affects a very small number of patients (about 6,000 in the United States).

ii) FDA Approval process

At present, the FDA has no mechanism for approving "generic" versions of biologic drugs (large-molecule or complex proteins that are synthetic or recombinant versions of natural biological substances), which are

regulated under Section 351 of the Public Health Service Act. The lack of a mechanism for approval of generic biologic products produces a unique situation in this class, with multiple competitive branded products available.

iii) Off-Label Uses

GH has the potential for substantial off-label use. It has been proposed as an anti-aging medication based on its effect on growth and metabolism. However, a systematic review found little evidence that GH is clinically beneficial in healthy elderly patients and substantial evidence suggesting high adverse event rates. The data did not support improvements in bone mineral density, lipid levels, or fasting glucose and insulin levels.

2) Efficacy

a) Efficacy Measures

The following measures are used as efficacy trial endpoints for both somatropin and mecasermin in growth-related condition:

- *Height expressed in centimeter (cm) or inches (in):* Absolute or change from baseline
- *Standard Deviation Score (SDS):* Actual height minus mean height for age divided by the standard deviation of height for age. The normal population mean is zero; a normal SD score will lie between -2 SD and +2 SD.
- *Final height:* Stipulates that the individual has stopped growing based on 1) the growth rate has slowed to less than 1-2 cm/year or 2) epiphyseal closure has occurred as confirmed by radiography
- *Near final height:* Based on height velocity less than a certain value, chronological age greater than 15-17 years, or skeletal age greater than 14-16 years
- *Height velocity:* Growth per period of time
- *Mid-parental height:* For boys, add 2.5 in or 6.5 cm to the mean of the parents' heights. For girls, subtract 2.5 in or 6.5 cm from the mean of the parents' heights. This sex-adjusted mid-parental height represents the statistically most probable adult height for the child, based on parental contribution.
- Predicted Adult Height (assuming no intervention): Predicted based on current height, age, and a set of tables known as the Bayley-Pinneau tables, which use radiographic bone age to determine growth potential.

b) Somatropin Efficacy

i) Introduction

GH (somatropin) treatment is indicated for treatment of a variety of conditions that largely affect linear growth. FDA indications overlap to

some degree (see Table 1). All products except Zorbtive and Serostim are indicated to treat GHD, but only three are indicated for treatment of short stature associated with Turner Syndrome, and only one is indicated for treatment of Prader-Willi Syndrome. However, treatment endpoints are similar across all growth-related conditions, and treatment goals are achieved by physiologic replacement or supplementation of growth hormone.

Of prescriptions filled by the Air Force High Dollar Program in July 2007, 62% were for pediatric GHD, another 16% were for adult GHD, 8% were for panhypopituitarism, 6% were for Turner Syndrome, and the rest were split out across various miscellaneous indications. While these data are limited, usage of the growth hormones products by age across the MHS confirms that the great majority of use is for pediatric indications (usage peaks in the 5-14 year age group), with some use in adults (45 years and older).

ii) Somatropin Clinical Efficacy

All marketed somatropin products contain recombinant human GH that is bioequivalent and equally biopotent, and are therefore unlikely to differ in efficacy for the treatment of growth related disorders. There are no studies that compare two or more somatropin products for any indication.

- *Treatment of Childhood Growth Disorders* – Published evidence supports clinical efficacy of somatropin in achieving growth-related clinical endpoints in these conditions, including GHD, Turner Syndrome, Prader-Willi Syndrome, growth restriction related to chronic kidney disease, and small for gestational age. Clinical endpoints evaluated in published clinical trials comparing GH to untreated controls have included: total gains in height, increases in growth velocity, and final or near final adult height vs. mid-parental height or normal population means.
- *Treatment of Adult GHD* – Published evidence supports the clinical efficacy of somatropin treatment in achieving various clinical endpoints, including improvements in body composition (reduction of fat mass, increases in lean body mass); modest reductions in cardiovascular risk factors such as blood pressure, total and LDL cholesterol, and triglycerides; and reduction of C-reactive protein. Modest improvements in bone mineral density (4-10% via DEXA) have also been shown. The data do not support clinically and statistically meaningful improvements in adults without GHD.
- *HIV/AIDS related wasting / cachexia and sShort Bowel Syndrome (SBS) in adults* – GH has been demonstrated to be efficacious in these conditions. The use of somatropin in AIDS wasting results in increased lean body mass and improved muscular strength and endurance, compared to untreated controls. No mortality benefit has been demonstrated. Treatment of SBS with somatropin is based on

evidence that somatropin accelerates the process of bowel adaptation. This process involves morphologic changes of the remaining bowel allowing it to have greater absorption of nutrients and fluids and lessen the need for parenteral nutrition. Data are limited, but suggest that up to four weeks of GH treatment has been beneficial in reducing the need for parenteral nutrition in SBS patients.

- *Noonan Syndrome and Short Stature Homeobox gene (SHOX) deficiency* – The FDA recently approved somatropin for use in two additional pediatric growth disorders: Noonan Syndrome and SHOX deficiency. Both of these conditions are genetic disorders associated with severely restricted growth. Published clinical trials have demonstrated significant improvements in growth-related endpoints in both conditions, compared to untreated control patients.
- *Idiopathic Short Stature (ISS)* – ISS, or non-GHD short stature, refers to individuals who are at least 2.25 standard deviations shorter than the mean height for sex and age (the shortest 1.2% of the population). These individuals have no identified physiologic abnormality affecting growth and appear to be healthy otherwise. Growth velocity and final height gains are modest even with somatropin treatment; individuals usually remain shorter than average regardless of treatment. There are no data showing that the gains in height following GH treatment are associated with improvements in quality of life or psychosocial functioning. Treatment of ISS is not considered medically necessary and is therefore not a covered benefit under TRICARE.

iii) Mecasermin Clinical Efficacy

FDA approval of mecasermin was based on the results of five clinical trials, which are unpublished but summarized in product labeling. These trials enrolled a total of 71 children (mean age 7 years) with symptoms of primary IGFD (slow growth rates, low IGF-1 serum concentrations, and normal GH secretion) and extreme short stature (height almost 7 SD below normal). For years 1 through 6, pooled results showed a significant increase in height velocity in mecasermin-treated patients, compared to baseline. Although statistical interpretation was complicated by the uncontrolled, longitudinal nature of the data and the varying lengths of exposure to mecasermin treatment (range <1 to 11.5 years), children appeared to gain, on average, an additional one inch per year for each year on therapy, compared to pretreatment growth patterns.

Bone age, relative to chronological age, was assessed in 49 subjects, since a disproportional acceleration of bone age (specifically epiphyseal closure) could lessen the eventual height reached even if the drug was otherwise effective at accelerating growth. Radiographically-assessed bone age advanced only marginally above chronologic age (4.9 $\pm$ 3.4 years mean $\pm$ SD change in chronological age vs. A 5.3 + 33.4 years change in bone

age). Subjects felt to be close to adult height all exceeded the mean height of untreated subjects, suggesting a positive net effect.

iv) GSA Efficacy Conclusion

Somatropin appears to be efficacious for the treatment of a number of growth-related disorders, including GHD, Prader Willi Syndrome, Turner Syndrome, chronic renal insufficiency, children who are small for gestational age, SHOX deficiency, and Noonan Syndrome, as well as non-growth related disorders, including adult GHD, AIDS/HIV wasting, and SBS. There are no studies that compare any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

Mecasermin increased height in children with severe IGFD, especially in the first year of administration, but not enough to bring these children close to the normal range. It is unlikely to be as effective as GH treatment for children who can respond to GH.

3) *Safety and Tolerability*

a) Somatropin

Mortality in children with GHD is due almost entirely to other pituitary hormone deficiencies. These children have an increased relative risk of death in adulthood from cardiovascular causes resulting from altered body composition and dyslipidemia. Adverse effects of somatropin appear to be dose-related. Initial somatropin studies used higher doses associated with many adverse effects; lower dosages are currently used.

i) Serious Adverse Effects

- *Pseudotumor cerebri or benign intracranial hypertension* – This is more common in children than adults; the FDA has received at least 23 reports in children, 1 in an adult. In all cases, symptoms of intracranial hypertension (headaches) resolved after discontinuation of GH therapy. Only a few patients experienced recurrent headaches and papilledema upon resuming therapy.
- *Slipped capital femoral epiphysis* – This condition is attributed to GH therapy, but may be linked to the result of diathesis induced by GHD and intensified by rapid growth. Children on GH therapy complaining of hip or knee pain should be carefully examined for slipped capital femoral epiphysis.
- *Patients with acute catabolism* – Use of somatropin products is contraindicated in this patient population, including preoperative and post-operative patients, critically ill patients, and burn patients. In a phase III prospective, randomized, placebo-controlled trial in Europe conducted in critically ill patients in an intensive-care unit facility,

patients were given 5.3 mg or 8 mg per day (weight-dependant) of GH therapy for 21 days. A significantly higher mortality (41.7% vs. 18.2%) was seen in the GH-treated group compared to placebo.

- *Retinopathy* is a rare complication of GH treatment. Three case reports (1 adult; 2 children) reported development of retinopathy following GH treatment, although one trial involving 85 children showed no retinopathy after 6.4 ± 2.9 years. A baseline funduscopic evaluation is recommended before starting GH treatment.
- *Malignancies* – Concern has surfaced about the association of GH treatment with tumor recurrence or development of malignancies. This has not been reported in adult GHD patients. An increase in leukemia was reported in Japanese pediatric GHD patients, although this was not confirmed by subsequent studies. Studies in the United States did not confirm an increase in frequency and have shown some differences in incidence related to other risk factors, for example, patients who previously received radiation therapy. This question remains unanswered.

ii) More Common Adverse Effects reported with somatropin include injection site reactions, hypothyroidism, transient gynecomastia, headaches, agitation, fatigue, seizures, and nausea/vomiting. Fluid retention and edema of the extremities, as well as arthralgia, myalgia, carpal tunnel syndrome, and blood pressure increases, are reported primarily in adults. GH may also be associated with insulin resistance and glucose intolerance. Some adverse effects appear to be dose-related.

Reported rates of adverse effects do vary from product to product, although this is potentially due to a number of factors, including differences in dosing regimens for specific indications, patient populations studied, or methods of collecting adverse effects. All products contain the same molecular entity (somatropin).

- *Fluid retention, edema, arthralgia, myalgia, and carpal tunnel syndrome* – Adult starting doses for GH were initially higher than those currently recommended. These higher doses were associated with fluid retention in conjunction with edema of the extremities, resulting in arthralgias, myalgias, and carpal tunnel syndrome. These adverse effects are more frequent in adults but do occur occasionally in GH-treated pediatric patients. In a study of 115 adult patients with GHD given GH therapy for 6 months, 37.4% developed edema, 19.1% developed arthralgia, 15.7% myalgia, 7.8% paresthesias, and 1.7% carpal tunnel syndrome. Most adverse effects occurred at the beginning of treatment and resolved within 1 to 2 months with continued treatment. Fluid retention can also cause increases in blood pressure.
- *Effects on blood glucose* – High doses of GH have been associated with hypoglycemia followed by hyperglycemia, since GH induces

transient resistance to the actions of insulin. In patients with limited insulin reserve, glucose intolerance may result. Insulin resistance and type 2 diabetes were reported in a few patients in early large clinical trials. A placebo-controlled GH trial reported that a higher number of patients receiving GH had worsening glucose tolerance compared to those receiving placebo, with impaired glucose tolerance seen in 13% and diabetes in 4% of GH patients.

iii) Contraindications – Somatropin is contraindicated in patients with active neoplasms or intracranial lesions and treatment should be stopped if evidence of tumor growth develops. Treatment should not be initiated in patients with proliferative or preproliferative diabetic retinopathy; Prader Willi Syndrome patients who are severely obese or have severe respiratory impairment; acute critically ill patients; and patients with growth-related disorders whose epiphyses have closed. Somatropin products containing the preservative benzyl alcohol are not suitable for use in newborns.

iv) Drug-Drug Interactions – Limited published data suggest that somatropin treatment increases CYP450-mediated antipyrine clearance in man. Somatropin may therefore alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, or cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. Formal drug interaction studies have not been conducted.

v) Tolerability – There is insufficient evidence to conclude that any one somatropin product is more tolerable or leads to better compliance than any other somatropin product. Any such differences are likely to be based on factors such as formulation / preservative differences and packaging.

Table 2: Somatropin Products – Other Consideration

Drugs	Preservative-free	Delivery Device			Storage		1-800 number
		Vial	Pen Device	Dose calculation to use pen	Ready to use	Room Temperature Storage	
Genotropin	yes		yes	Not required	Miniquick syringe only (single-dose)	Before initial use: Miniquick syringe	yes
Humatrope		yes	yes	Required			yes
Norditropin			yes	Not required	yes	After initial use: (21 days for Nordiflex 5 & 10 mg pens)	yes
Nutropin & Nutropin AQ		yes	yes	Required	yes		yes
Omnitrope	yes	yes		-			yes
Saizen		yes	yes, pen & needle-free pen	Required		Before initial use	yes
Serostim	yes	yes	yes, needle-free pen	Required		Before initial use	yes
Tev-Tropin		yes	*	-			yes
Zorbtive		yes		-			yes

*Approval of pen device anticipated

vi) *Other Considerations* – Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or vial/syringe); and storage requirements (refrigeration vs. room temperature). Table 2 outlines differences between somatropin products with regard to many of these issues.

- *Educational material* – All manufacturers provide some type of educational material for their products, ranging from a hotline number for information and assistance to the patient or caregiver (provided by all manufacturers) to complete packages including a hotline number, website, nurse educator for initial instruction, and a safety registry website for physicians. The literature assessing the value of these educational programs is sparse. In MTFs, certain components of the educational programs are handled by MTF staff and manufacturer offerings such as nurse educators may be of little additional value.
- *Formulations* – The primary reason for the selection of preservatives is to prevent leaching of the drug into its glass or plastic container. The availability of a preservative-free product may be an advantage, although the need for such a product for use in infants should be rare. In addition, ready-to-use formulations that do not require reconstitution may increase accuracy of dosing.
- *Delivery Devices* – Availability of a product in a pen device allows for accuracy in dosing and may enhance compliance. Pens are available for these product lines: Genotropin, Humatrope, Norditropin, and Nutropin. Providers in general reported that patients prefer pens to vials; indeed, 67% of MHS utilization from June 2006 to July 2007 was for pens, followed by vials (26%) and disposable syringes (7%).

  Some pen devices conceal the needle from view, an advantage in children who fear needles. The Serono products, Saizen and Serostim, are the only products with a needle-free pen device. An additional consideration is the requirement for dose calculations on the part of the caregiver/patient; some pens require users to convert the milligram dose prescribed to the units dosed on the pen. Products requiring conversions are the Nutropin product line, Saizen, and Serostim.
- *Drug Wastage* – Packaging for the two somatropin products that lack a GHD indication (Serostim and Zorbtive) is designed for dosage regimens used in AIDS/HIV wasting and SBS, not for use in GHD. Drug wastage would be inevitable if these products were used for GHD. In addition, educational materials available for these products do not address GHD.

b) Mecasermin

i) Serious Adverse Effects

- *Hypoglycemia* – Mecasermin can cause hypoglycemia due to its insulin-like effects. Hypoglycemia was reported in 30 of 71 patients in clinical trials (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five patients had severe hypoglycemia that required assistance and treatment on one or more occasion, while four experienced hypoglycemic seizures/loss of consciousness on one or more occasion. Of the 30 patients reporting hypoglycemia, 14 (47%) had a history of hypoglycemia before treatment. The incidence of hypoglycemia was highest in the first month of therapy, and episodes were more frequent in younger children. Symptomatic hypoglycemia was usually avoided when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of mecasermin.
- *Lymphoid tissue hypertrophy* – Hypertrophy of lymphoid tissues (e.g. Tonsillar) can result in snoring, sleep apnea, and chronic middle-ear effusions. Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1 to 2 years of therapy with lesser tonsillar growth in succeeding years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the surgery in all three cases.
- *Intracranial hypertension* – Intercranial hypertension with papilledema, visual changes, headache, nausea and/or vomiting have been reported with mecasermin (as with therapeutic GH administration). Intracranial hypertension occurred in three subjects, and in two subjects, resolved without interruption of mecasermin treatment. Mecasermin therapy was discontinued in the third subject and resumed later at a lower dose without recurrence.
- *Scoliosis* due to slipped capital femoral epiphysis can occur with rapid growth.

ii) Common Adverse Effects reported in the pooled mecasermin trials were hypoglycemia (42% of patients), lipohypertrophy, and tonsillar hypertrophy (15%). Other adverse effects occurring in at least 5% of patients include bruising, otitis media, headache, dizziness, convulsions, vomiting, hypoacusis, fluid in the middle ear, ear pain, abnormal tympanometry, arthralgia, pain in extremity, and thymus hypertrophy. Adverse effects were generally mild to moderate and no patients withdrew from the pooled trials as a result.

Also reported during clinical trials were: mild elevations in serum AST, alanine aminotransferase (ALT), and lactate dehydrogenase not leading to treatment discontinuation; increases in cholesterol and triglycerides to above the upper limit of normal; increases in renal and/or splenic length

reaching or surpassing the 95th percentile in some patients but not associated with impairments in renal function (as defined by serum creatinine and calculated creatinine clearance); echocardiographic evidence of cardiomegaly/valvulopathy without associated clinical symptoms ; and development of anti-IGF-1 antibodies with no apparent clinical consequence (e.g., allergic reactions or attenuation of growth).

iii) Contraindications – Mecasermin is contraindicated in patients whose epiphyses are already closed and those with active or suspected neoplasia. Mecasermin is not suitable for use in neonates due to its benzyl alcohol preservative.

iv) Monitoring – Preprandial glucose monitoring should be considered at treatment initiation, until a well tolerated dose is established, or if frequent or severe symptoms of hypoglycemia occur. Funduscopic exams are recommended at the start of therapy and periodically thereafter. Patients should also be monitored for *t*hickening of soft tissues of the face and symptoms suggesting the occurrence of scoliosis due to a slipped capital femoral epiphysis.

v) Special Populations – Safety and effectiveness has not been established in children less than 2 years of age or in adults.

c) Safety/Tolerability Conclusion

i) Growth Hormone (Somatropin)

Serious adverse events of GH include benign intracranial hypertension, slipped capital femoral epiphyses, and retinopathy. Whether or not GH treatment has tumorigenic effects remains debatable, due to possible associations with underlying disease states. The most common adverse events are edema, arthralgias, injections site reactions, diabetogenic effects, and hypothyroidism. Consistent lab monitoring is necessary to decrease the potential for adverse effects from possible excessive dosing or exacerbation of other disease states; required monitoring does not differ among marketed products. GH is not recommended in critically ill patients.

Although all products contain the same molecular entity, reported rates of adverse events vary from product to product, possibly due to different dosing schemes for specific indications or differences between study populations. There is limited evidence concerning differences between products attributable to excipients. Preservatives are primarily used as a way to prevent the drug leaching into the plastic or glass container. Products containing the preservative benzyl alcohol are not suitable for use in newborns; preservative-free products are available.

Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or

vial/syringe); and storage requirements (refrigeration vs. room temperature).

The biggest difference is in available delivery devices (e.g., a pen device, vial/syringe, needle-less system). A pen device is advantageous for ease of use and may increase accuracy in dosing. A pen device that does not require the caregiver or patient to convert from milligrams to "units" or "clicks" is more convenient and less likely to cause errors than one that requires conversion. Only one manufacturer, Serono, offers a needle-free device (for Saizen and Serostim).

Most of the products require refrigeration before and after initial use; products with room temperature storage may be advantageous in terms of limiting waste of the product and facilitating use while traveling. All products have a hotline number for patients and caregivers; other materials vary.

ii) Mecasermin

Mecasermin can cause disruptions in blood glucose and may require blood glucose monitoring. Lymphoid tissue hypertrophy, intracranial hypertension: and scoliosis due to slipped capital femoral epiphysis related to rapid growth can also occur.

4) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) Somatropin products appear to be safe and efficacious for the treatment of various growth-related conditions and for a few specialized non-growth related conditions.

b) There are no studies comparing any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

c) There are potential differences between somatropin products with respect to delivery devices, formulations, and stability/storage requirements. Differences that may favor particular products include availability of a pen device (preferably along with a vial/syringe product); the ability to use the pen device without having to do dose conversions, and the ability to store products at room temperature before or after initial use.

d) Mecasermin is safe and efficacious for severe IGF-1 deficiency, a much rarer condition than GHD. It is the only product available for the treatment of this condition.

e) Based on clinical issues alone, there are no compelling reasons to classify any of the GSA agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. GSAs – Relative Cost Effectiveness

In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The GSAs are divided into the IGF-1 and somatropin subclasses. The sole IGF-1 agent is mecasermin. It is indicated for the treatment of IGF-1 deficiency and therefore occupies a unique place in therapy within the GSAs. Among the somatropin products, two (Serostim and Zorbtive) are primarily used in disorders most commonly seen in adult patients (HIV wasting and short bowel syndrome). These two somatropin products are therefore available in dosage forms/ concentrations that would make delivery of a pediatric dose difficult. For these reasons, mecasermin, Serostim, and Zorbtive were excluded from the CMA and BIA. However, they were compared to the other GSAs on a cost per milligram basis.

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the remaining somatropin products within the GSA class differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of GHD. As a result, CMA was performed to compare the relative cost effectiveness of these somatropin products.

Results from the somatropin CMA revealed: 1) Tev-Tropin was the most cost effective somatropin product. However, Tev-Tropin does not offer some of the features (pen dosage forms, storage at room temperature, and ease of use) that some of the more costly products offer; 2) two product lines, Norditropin and Nutropin, are the most cost effective agents that offer physician- and patient-preferred features.

The BIA evaluated the potential impact of various scenarios with one or more somatropin products designated as formulary on the UF. The BIA included a single agent in front of a step-edit (automated PA) as well as two or more (up to all) somatropin products on the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Mecasermin and two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and are offer sufficient value on a cost/mg basis relative to the other agents within the therapeutic class.
2) Tev-Tropin was the most cost effective somatropin agent based on cost-minimization analysis. However, the product offers fewer features than most other growth stimulating agent product lines.
3) Two somatropin product lines, Norditropin and Nutropin, offered more features (pen dosage forms, storage at room temperature, and ease of use) at a middle range of cost.
4) The BIA results showed that the most cost effective formulary strategy for the somatropin products was the combination of the Tev-tropin and the Norditropin and Nutropin product lines.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the GSA relative cost effectiveness analysis as presented by the PEC.

C. GSAs – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the GSA agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that Tev-Tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and mecasermin be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary under the UF.

D. GSAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

The P&T Committee noted that since the somatropin products all contain the same active ingredient, the most likely scenario under which criterion #2 would apply would be issues specific to specific formulations / preservatives (e.g., injection site reactions).

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. GSAs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have the somatropin products Genotropin, Humatrope, Saizen and Omnitrope on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary Somatropin agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-

day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. GSAs – PA Criteria

Currently, PA criteria apply to both GH (somatropin products) and mecasermin. The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) that the following PA criteria should apply to GH and mecasermin. Changes from previous GH (somatropin) criteria are the addition of Noonan's Syndrome and SHOX deficiency as covered uses; no changes were recommended to mecasermin criteria.

1) *Growth Hormone (Somatropin)* – Coverage would be approved for the treatment of any of the following:
   a) GHD in children and adults as a result of pituitary disease, hypothalamic disease, surgery or radiation therapy
   b) Chronic renal insufficiency before renal transplantation with associated short stature
   c) Other known renal indications: autorecessive polycystic kidney disease, cystinosis and hypophosphatemic rickets in the pediatric population
   d) Short stature in patients with Turner Syndrome or Prader-Willi Syndrome
   e) Infants born small for gestational age that have not reached age appropriate height by 24 months of age
   f) Human immunodeficiency virus-associated wasting in adults
   g) Noonan Syndrome
   h) SHOX deficiency
2) *Mecasermin* – Coverage would be approved for the treatment of:
   a) Patients with severe primary IGFD defined by the following:
      i) Height standard deviation score $\leq$ -3
      ii) Basal IGF-1 standard deviation score $\leq$ -3
      iii) Normal or elevated GH levels

      OR
   b) Patients with GH gene deletion who have developed neutralizing antibodies to GH

   In addition, patients must meet the following criteria:

   - Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders (e.g., pediatric endocrinologist)
   - Thyroid and nutritional deficiencies have been corrected before initiating mecasermin treatment
   - Have been educated on monitoring and management of hypoglycemia

Coverage is NOT provided for:

- Patients with closed epiphyses (bone growth plates)
- Patients with active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops)
- Patients with other causes of growth failure (secondary forms of IGF-1 deficiency, such as GHD, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroid

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

G. GSAs – Extended Core Formulary (ECF) Review and Recommendations

The P&T Committee considered the ECF status of the GSA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin / Norditropin Nordiflex be added to the ECF.

9. QUANTITY LIMITS

A. Rizatriptan (Maxalt) – The current QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 18 tablets per 30 days, or 36 tablets per 90 days. This QL was increased from 12 to 18 tablets per 30 days in May 2006 to accommodate a change in packaging (from 6 tablets per package to 9 tablets per package). Packaging for rizatriptan recently changed again, from 9 tablets per package to 12 tablets per package. QLs for triptans are based on the lack of safety evidence for treating more than 3-4 headaches per month with triptans, dosing recommendations, and package size.

***COMMITTEE ACTION*:** The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets to 12 tablets per 30 days, or 36 tablets per 90 days.

10. BCF STATUS OF ROSIGLITAZONE

Rosiglitazone (Avandia) – The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone.

1) *FDA Alert #1: 8/14/2007:* Important revisions to the full prescribing information (labeling) highlighting increased risks of congestive heart failure associated with rosiglitazone. The updated information includes a new BOXED WARNING, and additional updated WARNINGS, PRECAUTIONS and CONTRAINDICATIONS to emphasize that rosiglitazone may cause or exacerbate heart failure, particularly in certain patient populations. *Source*: www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

2) FDA Alert #2: 5/21/2007**:** Ongoing FDA review of clinical data to assess a potential increased risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA is aware of a potential safety issue related to rosiglitazone maleate. Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking rosiglitazone.

However, other published and unpublished data from long-term clinical trials of rosiglitazone provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label. FDA does not know whether the other approved medication in the same pharmacologic class or other oral drugs for treating type 2 diabetes have less, the same, or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions. *Source:* www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more information becomes available.

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to not remove rosiglitazone from the BCF at this time.

11. BCF / ECF REVIEW

The P&T Committee agreed with the PEC's plan to systematically review drug classes represented on the BCF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review. The P&T Committee agreed that BCF/ECF listings will in the future be framed with greater specificity as drug classes are reviewed or reviewed.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate/vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine). Details are outlined in Appendix C.

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings (see Appendix C for rationale):

Table 3: Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

12. CLASS OVERVIEWS

Class overviews for the osteoporosis agents were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the February 2008 meeting; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 15 August 2007. The next meeting will be 14-15 November 2007.

_____// signed // _____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	Pending approval	Pending approval
Aug 07	Leukotriene Modifiers	▪ Zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	Pending approval	Pending approval
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	Pending approval	Pending approval
Nov 05 (updated for new drug Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended Aug 07 ▪ fluticasone furoate (Veramyst)			Pending approval	Pending approval
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg rospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. August 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Budesonide / formoterol inhaler (Symbicort, Astra Zeneca) corticosteroid with long-acting beta agonist	Jul 06 (launched Jul 07) ▪ Long term maintenance treatment of asthma in patients 12 years of age and older.	No UF recommendation at this meeting. Consideration of UF status deferred until inhalational asthma drugs are reviewed; UF review anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o #3 inhalers per 90 days ▪ Retail Network o #1 inhaler per 30 days
Rotigotine topical patch (Neupro; Schwarz Biosciences) non-ergoline D3/D2/D1 dopamine agonist	May 07 (launched Jul 07) ▪ Treatment of signs and symptoms of early stage idiopathic Parkinson's disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's drugs are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.1% gel (Divigel; Upsher-Smith) estrogen for hormone replacement	Jun 07 (launched Aug 07) ▪ Treatment of moderate to severe hot flashes associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.06% gel (Elestrin; Bradley Pharmaceuticals) estrogen for hormone replacement	Dec 06 (launched Jun 07) Treatment of moderate to severe vasomotor symptoms associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.

Appendix C – Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF / ECF listing	Recommendation/ Rationale
Atypical antipsychotics	BCF – "Quetiapine"	• ER formulation (Seroquel XR) approved May 07; manufacturer willing to supply at no higher cost than IR quetiapine; no generics anticipated for some time (~2011). • Available in IR tabs (6 strengths), ER tabs (4 strengths). • Recommendation: • Clarify BCF listing to "Quetiapine tablets, immediate and extended release."
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	• Oral dosage forms available: solution, tablets (6 strengths), rapidly disintegrating tablets (5 strengths) • Several manufacturers have tentative ANDAs listed for risperidone solution and tablets; patent expires Dec 2007, pediatric exclusivity ends Jun 2008. Unclear when orally disintegrating tablets will become generically available. • Recommendation: • Clarify BCF listing to "Risperidone tablets and solution, does not include orally disintegrating tablets."
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	• Alendronate 70 mg / vitamin D 5600 IU approved Apr 07; manufacturer willing to extend current pricing agreement for Fosamax Plus D; class to be reviewed soon. • 5600 IU combination recommended for "most" osteoporotic patients. • Recommendation • Clarify BCF listing to specify product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets."
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral" (Entex LA generic)	• Guaifenesin containing timed release prescription products targeted for regulatory action by FDA in May 2007. • Companies expected to stop manufacturing unapproved products containing timed-release guaifenesin within 90 days and must cease shipping them in interstate commerce within 180 days. • Only guaifenesin products expected to remain on market are Adams' Labs over-the-counter products (e.g., Mucinex D). • Recommendation: • Remove listing from BCF.

Appendix D – Table of Abbreviations

ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ALT	alanine aminotransferase
APR	automated profile review
ARB	angiotensin receptor blocker
AR	allergic rhinitis
ARIA	Allergic Rhinitis and Its Impact on Asthma
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BP	blood pressure
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CIU	chronic idiopathic urticaria
CMA	cost minimization analysis
CRI	chronic renal insufficiency
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DoD	Department of Defense
EIB	exercise-induced bronchoconstriction
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FY	fiscal year
GAD	generalized anxiety disorder
GH	growth hormone
GHD	growth hormone deficiency
GI	gastrointestinal
GSA	Growth Stimulating Agent (drug class)
HCTZ	hydrochlorothiazide
IGFD	insulin-like growth factor deficiency
ICS	inhaled corticosteroids
ISS	idiopathic short stature
LABA	long-acting beta agonists
LDL	low density lipoprotein
LFT	liver function test
LM	Leukotriene Modifier (drug class)
MAOI	monoamine oxidase inhibitor
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
NA	Newer Antihistamine (drug class)
NCS	nasal corticosteroids
NHLBI NAEPP	National Heart, Lung and Blood Institute National Asthma Education Prevention Program
OTC	over-the-counter
PA	prior authorization
PAR	perennial allergic rhinitis
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center

Appendix D – Table of Abbreviations (continued)

QD	once daily
QID	four times daily
RAAs	renin-angiotensin antihypertensive (drug class)
RCT	randomized controlled trial
RQLQ	rhinoconjunctivitis-specific quality of life
RR	relative risk
rTNSS	reflective Total Nasal Symptom Score
SAR	seasonal allergic rhinitis
SBS	Short bowel syndrome
SED-1	Sedative Hypnotic-1 (drug class)
SGA	small for gestational age
SHOX	Short Stature Homeobox gene
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TID	three times daily
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TNSS	Total Nasal Symptom Score
TRRx	TRICARE Retail Pharmacy Network
TS	Turner Syndrome
UF	Uniform Formulary
ULN	upper limit of normal

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2007

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Pharmacy and Therapeutics (P&T) Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or prior authorization (PA) requirements for the drugs (see paragraph 5A on pages 19-20 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Arformoterol (Brovana) –The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.
- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Over-the-Counter Terbinafine 1% Cream (Lamisil AT) – The John Warner National Defense Authorization Act for FY 2007 directs the Secretary of Defense to conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program Office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the demonstration.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole (Lotrimin, generics) and nystatin (Mycostatin, generics) are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

Relative Clinical Effectiveness – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF (butenafine and naftifine). The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the other prescription allylamines for the treatment of common dermatologic infections.

Relative Cost Effectiveness – Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

COMMITTEE ACTION: UF RECOMMENDATION –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – ANTILIPIDEMIC II AGENTS (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants (BAS). The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate (Tricor, Lofibra, Antara, and Triglide). Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF. The BAS class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Fibric acid derivatives

   a) Both gemfibrozil and fenofibrate reduce triglycerides (TG) by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

   b) Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI ($p=0.01$) and coronary revascularization ($p=0.035$).

   c) Although gastrointestinal (GI) adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data from product labeling. Gemfibrozil must be taken twice daily prior to meals.

   d) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a

statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

e) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the National Heart Lung and Blood Institute conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

f) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

2) Omega-3 Fatty Acids (Omacor)

a) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

b) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in low density lipoprotein (LDL), which may offset beneficial reductions in TG.

c) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

d) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

3) Bile Acid Sequestrants

a) The BAS agents reduce LDL by 15 to 30%. This subclass has largely been replaced by the statins, which reduce LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL.

Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

b) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

c) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

d) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the pharmacoeconomic analyses and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Gemfibrozil was the most cost-effective fibric acid derivative evaluated. Of the various fenofibrate formulations, IDD-P fenofibrate demonstrated the best cost effectiveness profile.

2) Colesevelam was recognized as not cost effective in the treatment of hyperlipidemia compared to other BAS.

3) In the management of hypertriglyceridemia, Omacor was identified as not cost-effective compared to gemfibrozil, fenofibrate, and niacin.

4) The UF scenario that maintained fenofibrate, IDD-P fenofibrate, cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate, IDD-P fenofibrate, cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00 (see paragraphs 6A, 6B, and 6C on pages 22-37 of the P&T Committee minutes).

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that “when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate.” The objective is to maximize use of IDD-P fenofibrate in the retail network and mail

order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor (see paragraph 6D on page 37 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 6E on pages 37-38 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: for 120 days

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class (see paragraph 6F on page 38 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs). The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). Both have been approved by the FDA for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The 5-ARI drug class accounted for $31.2 million in MHS expenditures for FY 2006 and is ranked #50 in terms of total expenditures. More than 281,000 prescriptions for 5-ARIs

were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of acute urinary retention and BPH-related surgery.
2) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum dihydrotestosterone levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (the Enlarged Prostate International Comparator Study) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.
3) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial); there are no published long-term combination trials with dutasteride.
4) The overall effect of 5-ARIs on prostate cancer prevention is unclear.
5) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.
6) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.
7) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.
8) Neither agent appears to interfere with prostate cancer detection.
9) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Finasteride was the most cost effective agent, with a lower cost per day of treatment than dutasteride across all condition sets evaluated.

2) A cost-effectiveness analysis that evaluated the cost per BPH surgery averted showed that finasteride was the preferred choice with a lower expected cost per surgery averted than dutasteride.

3) The UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that: 1) finasteride be classified as formulary on the UF, and 2) that dutasteride be classified as non-formulary under the UF (see paragraphs 7A, 7B, and 7C on pages 38-44 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for dutasteride and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for dutasteride (see paragraph 7D on page 44 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 44-45 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating finasteride as the BCF selection in this class (see paragraph 7F on page 45 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting.

PPIs have become the standard of care for treatment of acid-related gastrointestinal disorders. As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class has now taken over the #1 spot in terms of MHS expenditures: more than $485 million over the 12 months from April 2006 to March 2007, compared to about $350 million in FY 2005. Military treatment facility (MTF) pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TRICARE Mail Order Pharmacy (TMOP). Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

2) Although some trials appear to demonstrate superior efficacy for healing of erosive esophagitis (EE) with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

3) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

4) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease and/or non-steroidal anti-inflammatory drug (NSAID) induced ulcers.

5) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of endoscopy-negative reflux disease (ENRD); there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

6) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

7) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

8) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

9) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) that:

1) The CMA of each potential UF scenario showed that, as expected, the more restrictive the UF scenario, the lower the cost per day of treatment.

2) Among UF scenarios with two agents on the UF, omeprazole and esomeprazole were the most cost effective option.

3) Among UF scenarios with three to four agents on the UF, omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

4) The UF scenario that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a PA requiring a trial of either agent for new patients was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the

purchased care arena (see paragraphs 8A, 8B, and 8C on pages 46-53 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: PA CRITERIA

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:
   a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
2) PA criteria if automated criteria are not met:
   a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
   b) Treatment with omeprazole or esomeprazole is contraindicated.

(See paragraph 8D on pages 53-54 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate (see paragraph 8E on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8F on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class (see paragraph 8G on page 55 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period.

The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure, and type 2 diabetic nephropathy.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.
2) Although losartan is labeled to reduce the risk of stroke in patients with left ventricular hypertrophy (LVH), Joint National Commission (JNC) guidelines support use of other antihypertensive drugs (e.g., angiotensin converting enzyme (ACE) inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.
3) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing heart failure (HF) hospitalizations in patients with chronic HF.
4) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of end stage renal disease) in patients with type 2 diabetic nephropathy.
5) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with left ventricular systolic dysfunction (LVSD).

However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

6) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

7) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) A UF scenario with three or fewer agents on the UF was more cost effective than scenarios that included additional agents on the UF.

2) Telmisartan was the most cost effective agent for the management of hypertension; candesartan was more cost effective for management of chronic HF than valsartan; losartan and irbesartan had similar cost effectiveness profiles for treatment of type 2 diabetic nephropathy.

3) The UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario evaluated.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 55-61 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ (see paragraph 9D on pages 61-62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9E on pages 62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF (see paragraph 9F on page 62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows

10. QUANTITY LIMITS

The P&T Committee agreed that current QLs for two nasal inhalers should be increased, based on daily maximum doses recommended in product labeling and increases in QL override requests based on higher dosing consistent with labeling (see paragraph 10 on pages 63-64 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Mometasone nasal spray (Nasonex) – The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (retail network pharmacies), 102 gm (6 inhalers) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.
- Ipratropium nasal spray (Atrovent) – The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (retail network pharmacies), 6 inhalers (180 mL) per 90 days (mail order); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45 mL) per 30 days (retail network pharmacies), 9 inhalers (135 mL) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents on the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the Beneficiary Advisory Panel (BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, it is not expected the item will normally generate further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and the drug had not been excluded from the UF based on clinical issues alone.
2) The non-formulary agent becomes generically available and:
    a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system

b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.

3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:

a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

(See paragraph 11 on pages 64-65 of the P&T Committee minutes).

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

S. Ward Casscells
24 July 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
May 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 15-16, 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL David Estroff, MC *for* COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA

D. Non-Voting Members Absent

LT Thomas Jenkins, MSC, USN	TMA Aurora
Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Lisa Longo, Pharm.D.	VAPBM
Lisa McNair	TMA
LCDR Rob Hayes	DHHS, Indian Health Service

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – February 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of February Minutes – MG Elder Granger, USA, MC, Deputy Director, TMA, approved the minutes of the February 2007 DoD P&T Committee meeting on May 2, 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss briefed the members of the P&T Committee regarding the March 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Administrative Action – Modification of Modafinil (Provigil) Prior Authorization (PA) Criteria – A PA for modafinil (Provigil) was recommended by the P&T Committee at the November 2006 meeting and subsequently approved by the Director, TMA, with an effective date of April 18, 2007. The PEC briefed the members of the P&T Committee on an administrative action to omit the PA criterion addressing use for cocaine dependence from PA criteria posted on the TRICARE Pharmacy website and incorporated into PA forms. The criterion provided for coverage of modafinil for cocaine dependence, based on two randomized trials supporting the use of modafinil for the treatment of cocaine dependency. (One trial reported decreased euphoria with cocaine use, the other an increased abstinence rate; modafinil is thought to counteract the glutamate-depleting effect of cocaine, possibly reducing craving.) The criterion was administratively omitted because coverage of substance abuse treatment in settings other than authorized institutional providers falls under another TRICARE approval process and is affected by other TRICARE regulations, not because of clinical considerations. The P&T Committee concurred with the change.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or PA requirements for the drugs.

The P&T Committee agreed that the three new drugs required QLs, based on existing QLs for similar agents (oral cancer agents and products for oral inhalation) and recommendations for use in product labeling.

COMMITTEE ACTION: QLs

- Arformoterol (Brovana) – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol (Brovana) of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.

- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib (Tykerb) as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat (Zolinza) as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

B. Over-the-Counter (OTC) terbinafine 1% Cream (Lamisil AT)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. The purpose is to assess the impact of authorizing TRICARE coverage for OTC agents recommended for inclusion on the UF. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product. OTC drugs provided under the demonstration project shall be made available through military treatment facilities (MTFs) and the TRICARE Mail Order Pharmacy (TMOP).

The P&T Committee, after consultation with the TMA Pharmacy Program office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the project. Since this is the first opportunity for terbinafine 1% cream OTC to be considered for UF inclusion, it was reviewed as a new drug in a class previously reviewed.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole and nystatin are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

1) *Relative Clinical Effectiveness* – Terbinafine is a synthetic allylamine derivative that interferes with synthesis of the fungal cell wall. Terbinafine was originally available as a prescription product in 1992, but as of 1999 is solely available OTC. FDA-approved indications for terbinafine include tinea pedis, tinea cruris, and tinea corporis. Terbinafine is also effective for treating tinea versicolor, although it is not labeled for this indication. Dosing and administration vary with the indication; for tinea pedis, terbinafine is applied twice daily for seven days, or once daily for four weeks. For tinea versicolor, tinea corporis, or tinea cruris, the

recommended dosing is once daily for 14 days. Terbinafine 1% OTC is available in several different formulations, including cream, spray, and gel; only the cream is under consideration for UF inclusion.

Allylamines on the UF include butenafine (Mentax) and naftifine (Naftin). The allylamines, including terbinafine, appear to be slightly more efficacious than azoles for treatment of tinea pedis. A Cochrane analysis evaluated efficacy of the allylamines (terbinafine, naftifine) and azoles (clotrimazole, econazole, miconazole, and sulconazole) for treating tinea pedis. Pooled analyses of trials comparing azoles with allylamines yielded cure rates of 73% with the azoles vs. 80% with the allylamines. There were no detectable differences in efficacy between individual allylamines or individual azoles.

In general, topical antifungals are recognized as safe and well-tolerated, allowing for the switch from prescription to OTC status for terbinafine. Common adverse events reported with terbinafine include burning, stinging, peeling or other local reactions, which are commonly attributed to the vehicle or the condition itself; terbinafine does not appear to be any more likely to cause these adverse reactions than the other allylamine products on the UF.

Conclusion: The P&T Committee concluded that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF. The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the prescription allylamines for the treatment of common dermatologic infections.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of terbinafine 1% cream OTC in relation to efficacy, safety, tolerability, and clinical outcomes of the other allylamines in the topical antifungal class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that terbinafine 1% cream OTC has similar efficacy, safety, tolerability, and clinical outcomes compared to the other allylamines in the topical antifungal class.

   The cost review for terbinafine 1% cream OTC compared the Federal Supply Schedule cost per 30 grams to the other allylamines, naftifine and butenafine.

   Conclusion: The results of the cost review showed that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

3) *Clinical and Cost Effectiveness Conclusions* – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional

judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF for the OTC Demonstration Project.

4) *Medical Necessity (MN) Criteria* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – ANTILIPIDEMIC AGENTS II (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants. Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF.

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures. By comparison, the LIP-1 drug class reviewed in August 2006 (statins, ezetimibe, niacin, and combinations) accounted for $500 million in MHS expenditures and was ranked #1.

A. LIP-2s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the LIP-2 agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 1: Antilipidemic II Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Fibric Acid Derivatives	Gemfibrozil	Lopid, generics
	Fenofibrate	
	Nanocrystallized	Tricor
	Non-micronized/micronized	Lofibra (generic to innovator Tricor)
	Micronized	Antara
	IDD-P (micronized)	Triglide
Omega-3 fatty acids	Omega-3 fatty acid	Omacor
Bile Acid Sequestrants	Cholestyramine/aspartame	Questran Light, Prevalite, generics
	Cholestyramine/sucrose	Questran, generics
	Colestipol	Colestid, generics
	Colesevelam	Welchol

IDD-P = Insoluble Drug Delivery - microParticle

1) Formulations

a) Fibric Acid Derivatives

i) Products

The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate. Fenofibrate is a prodrug that is metabolized to its active ingredient, fenofibric acid. The innovator fenofibrate product launched in 1998 under the trade name Tricor by Abbott Laboratories was very insoluble in water, thus was poorly absorbed and required administration with food. Drug particle size has been reduced in newer fenofibrate formulations to enhance absorption compared to the original fenofibrate product. As products are re-formulated, previous versions are typically removed from the market.

The most recent fenofibrate formulations are micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide), and nanocrystallized fenofibrate (Tricor). Antara, Triglide, and Tricor can be taken without regard to meals.

The innovator fenofibrate formulation has been discontinued by Abbott, along with a later version. The current Tricor product (nanocrystallized) is the third version on the market. Lofibra is a branded generic to the two earlier Tricor formulations, and is available in both a micronized and non-micronized version.

ii) FDA approval process

The newer fenofibrate formulations received FDA approval via a 505b(2) application. Under this process, newer products are approved by demonstrating bioequivalence to the original new drug application of the innovator fenofibrate 200 mg product. The newer formulations are marketed in varying dosage strengths lower than 200 mg. However, bioequivalence is similar between innovator fenofibrate 200 mg, IDD-P micronized fenofibrate (Triglide) 160 mg, nanocrystallized fenofibrate 145 mg, and micronized fenofibrate (Antara) 130 mg.

b) Omega-3 Fatty Acids

i) Products

Fish oil Supplements – The omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several formulations of omega-3 fatty acids (fish oils) are available as dietary supplements. Dietary products do not undergo the rigorous approval process required for prescription products.

Prescription omega-3 fatty acids (Omacor) – Omacor is a marine-derived omega-3 polyunsaturated fatty acid product that was approved by the FDA in 2004. It is the first and only prescription fish oil product available. Each 1-gram Omacor capsule contains 90% omega-3 acid esters,

consisting of 465 mg (46%) EPA, 375 mg (38%) DHA), 6% other omega-3 acid esters, and 10% omega-6 fatty acids.

ii) FDA indication

Fish Oil Supplements – The FDA allows a qualified health claim for dietary supplements and conventional foods containing EPA and DHA omega-3 fatty acids to reduce the risk of coronary heart disease (CHD).

Omacor – Omacor is currently approved only as an adjunct to diet in patients with very high triglyceride (TG) levels (>500 mg/dL).

iii) Off-label uses

Prevention of CHD – In Europe, fish oil supplements are approved by regulatory authorities for secondary prevention of CHD. The U.S. FDA has not approved use of the Omacor product for CHD prevention, as it considers the data incomplete. In February 2007, the manufacturer added wording to the labeling stating that Omacor has not been shown to prevent myocardial infarction (MI) or strokes. However, Omacor is likely to be used off-label for CHD prevention.

c) Bile Acid Sequestrants

i) Products – The bile acid sequestrants (BAS) have been marketed since the 1960s and are still utilized for lowering low density lipoprotein (LDL). The class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

ii) Indications – The BAS are all indicated for use as either monotherapy or in combination with statins to reduce LDL.

iii) Pharmacokinetics – The BAS are not absorbed and are not hydrolyzed by digestive enzymes. The older agents preferably bind to dihydroxy bile acids over trihydroxy bile acids. Colesevelam binds to both dihydroxy and trihydroxy bile acids equally, thus removing both types of bile acids from the circulation. *In vitro* lab data suggests that colesevelam is 4 to 6 times more potent than the older BAS in regard to lower total cholesterol and LDL levels, possible due to enhanced binding of trihydroxy bile acids. However, this difference in *in vitro* binding has not translated into enhanced efficacy of colesevelam in clinical trials assessing lipid parameters.

2) Efficacy

a) Efficacy Measures

The primary efficacy measures used to assess efficacy of the LIP-2 agents are reduction in LDL, TG, and total cholesterol levels (TC), and increases in high-density lipoprotein (HDL). The fibric acid derivatives and omega-3 fatty acids primarily reduce elevated TG levels and raise HDL. The BAS primarily reduce LDL.

When available, clinical outcomes data (reduction of CHD risk, including MI, mortality (all-cause or CHD), need for revascularization, and stroke) were also evaluated to assess differences between agents.

b) Fibric Acid Derivatives

i) Lipoprotein efficacy

Package inserts – The majority of clinical trials evaluating lipid effects have compared gemfibrozil or fenofibrate (Tricor, Antara, Triglide, Lofibra) with placebo. Both fenofibrate and gemfibrozil reduce TG levels by 20 to 50% and increase HDL by 10 to 20%. Varying effects on LDL concentrations are seen, ranging from reductions to increases of 5 to 20%.

Head-to-head trial – One small comparative trial with the fibric acid derivatives is available. Micronized fenofibrate 200 mg (an earlier Tricor formulation) was compared to gemfibrozil in 21 patients with type IIa and IIb hyperlipidemia. After six weeks, similar reductions in triglycerides were seen between the two agents (54% with fenofibrate vs. 46.5% with gemfibrozil; not statistically significant). However, micronized fenofibrate resulted in greater reductions in LDL and TC than gemfibrozil. The differences in LDL effects were likely attributed to the fact that a gemfibrozil dose of 900 mg QD was used, rather than the FDA-approved 600 mg BID dosage.

ii) Clinical outcomes

Three placebo-controlled trials are available that assessed clinical outcomes for gemfibrozil (HHS, VA-HIT) and fenofibrate (FIELD). There are no published head-to-head trials available that assess clinical outcomes (e.g. all-cause mortality, CHD mortality, MI, etc).

- *Helsinki Heart Study 1987 (HHS)* – HHS was a double-blind, placebo-controlled study conducted in 4,000 Finnish men (average age 47 years) who did not have CHD (primary prevention trial). After five years, gemfibrozil 600 mg BID resulted in a significant reduction (34%) in nonfatal MI and CHD death, compared to placebo. There was no difference between gemfibrozil and placebo in all-cause mortality.
- *Veteran Affairs High density lipoprotein cholesterol Intervention Trial 2001 (VA-HIT)* – VA-HIT was a secondary prevention trial conducted in over 2,000 male VA patients who had a history of CHD (average age 64 years). After five years, compared to placebo, treatment with gemfibrozil 600 mg BID resulted in a significant reduction (22%) in the risk of nonfatal MI or CHD death. There was no difference in death due to any cause. Thirty percent of the study participants were diabetic, and when this subpopulation was analyzed, significant reductions in the composite of nonfatal MI, stroke and CHD death were seen.

- *Fenofibrate Intervention and Event Lowering in Diabetes 2005 (FIELD)* – The FIELD trial was a randomized double-blinded placebo-controlled trial which included 9,975 type 2 diabetic participants, 2,131 of whom had cardiovascular disease. Patients were treated with fenofibrate 200 mg QD or placebo for 5 years. Patients were not receiving statins at the start of the study, but could start antilipidemic therapy, including statins, during the trial.

  After five years, there was no statistically significant difference between fenofibrate and placebo in the primary composite endpoint of nonfatal MI and CHD death (5.9% vs. 5.2%, respectively, hazard ratio 0.89, 95% CI 0.75-1.05). However, statistically significant reductions in nonfatal MI (4% vs. 3%) and total cardiovascular events (14% vs. 13%) were seen with fenofibrate. Reductions in total cardiovascular events were primarily due to a significant reduction in the need for coronary revascularization (7% vs. 6%). The concomitant use of statins in 17% of the placebo group vs. only 8% of the fenofibrate group may have accounted for the modest effect of fenofibrate in reducing cardiovascular events.

  An unexpected finding was a 19% (p=0.22) increase in CHD death with fenofibrate compared to placebo, reflecting an increase in sudden deaths in the fenofibrate group.

iii) Efficacy conclusion

Clinically the fibric acid derivatives are useful in reducing elevated TG concentrations and raising HDL. There are no major clinical differences between gemfibrozil and fenofibrate in terms of changes in lipid parameters as shown in the HHS, VA-HIT and FIELD clinical trials; both drugs reduce TG by 20-50%, and increase HDL by 10-20%. Varying effects on LDL have been reported. One small head-to-head trial reported that fenofibrate resulted in greater reductions in TG and LDL than gemfibrozil; however, the gemfibrozil dose was lower than that recommended in the product labeling.

Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI and coronary revascularization.

b) Omega-3 fatty acids

i) Lipoprotein efficacy

Fish oil supplements: placebo-controlled trials – One meta-analysis of 36 crossover and 32 parallel studies of dietary and supplemental omega-3 fatty acids reported that a 3- to 4-gram daily dose resulted in a reduction of TG by

25-34%, and an increase in LDL by 4-11%, regardless of source or formulation.

Omacor: placebo-controlled trials – Ten prospective, randomized clinical trials have examined the effects of the marketed Omacor formulation on TG and LDL concentrations in patients with elevated TG levels. Overall, Omacor 4 grams daily resulted in a 20-45% reduction in TG levels when compared to placebo. The TG-lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG-lowering response).

Increases in LDL ranging from 17 to 31% were reported in four of the ten studies. Increases in LDL also appeared to correlate with baseline TG levels. Concomitant use of a statin may blunt any increase in LDL associated with Omacor.

ii) Omacor vs. fish oil supplements – There are no head-to-head trials comparing the lipid effects of Omacor vs. nutritional omega-3 fatty acid supplements.

iii) Omacor vs. other lipid-lowering therapies – The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin.

iv) Clinical outcomes

- *Fish oil supplements: systematic reviews/meta-analyses* – The effects of dietary or supplemental omega-3 fatty acids on cardiovascular disease outcomes have been evaluated in several meta-analyses and systematic reviews, with conflicting results reported. Some reports suggest a beneficial effect when omega-3 fatty acids are used for either primary or secondary cardiovascular disease prevention. In contrast, a 2004 Cochrane review of randomized controlled trials and cohort studies found no strong evidence that dietary or supplemental omega-3 fatty acids reduced total mortality, cardiovascular events, or cancer.
- *Fish oil supplements: placebo-controlled trial (GISSI-Prevenzione)* – In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione Trial, an omega-3 fatty acid with a different ratio of EPA and DHA than Omacor was evaluated. Fish oil supplementation was associated with a 15% reduction in the risk of the composite endpoint of death, nonfatal MI, and stroke in 11,324 survivors of a recent MI. There was a 20% reduction in all-cause mortality, which was driven by a 45% reduction in sudden death. There was no difference in nonfatal MI between the groups. Limitations to the study include the open label study design, a dropout rate nearing 30% by study completion, use of a fish oil supplement different than Omacor, and high dietary intake of fish (which in itself has cardiovascular benefits).

- *Omacor: placebo-controlled trial* – One placebo-controlled, double-blinded trial evaluated the effect of Omacor on cardiovascular outcomes. In this study, 300 patients with acute MI were randomly assigned to receive Omacor 4 grams daily or corn oil placebo for a median time period of 1.5 years. There was no statistically significant difference in the rate of cardiac events (cardiac death, resuscitation, recurrent MI, and unstable angina) between groups (28% with Omacor vs. 24% with placebo, hazard ratio 1.19, 95% CI 0.76-1.86). The lack of difference was attributed to the small size and short duration of the trial, as well as the inclusion of Norwegian patients whose diets already contained a high content of fish.
- *Omacor vs. fish oil supplements* – There are no head-to-head trials of Omacor versus fish oil supplements.
- *Omacor vs. other lipid-lowering therapies* – Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

v) Efficacy conclusion: Randomized clinical trials showed a reduction in TG levels of 20-45% with Omacor 4 grams once daily. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG. Concomitant use of a statin may blunt increases in LDL.

The GISSI-Prevenzione trial is the largest trial showing a benefit of omega-3 fatty acids on cardiovascular outcomes, but it assessed a different omega-3 fatty acid product and not Omacor. Its validity may also be limited by its open-label design, high dropout rate, and high dietary fish intake. A small, short-duration placebo-controlled trial specifically assessing the cardio-vascular outcomes of Omacor did not demonstrate a reduction in cardiac events.

The TG-lowering effect of Omacor is slightly less than that achieved with either fibric acid derivatives or niacin. In the National Cholesterol Education Panel (NCEP) guidelines, fibric acid derivatives or niacin are listed as first-line treatments for patients with TG >500 mg/dL; both have clinical outcomes data supporting a benefit in reducing the risk of cardiovascular events.

c) Bile Acid Sequestrants

i) Lipoprotein efficacy – There are only a few clinical trials available for the BAS, and most were conducted in the 1970s and early 1980s. No trials have compared the older agents, cholestyramine and colestipol, with colesevelam.

- *Cholestyramine* – The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a large placebo-controlled trial that compared cholestyramine 24 g QD to placebo in preventing coronary artery disease (CAD) in 3,806 men with primary hypercholesterolemia. Treatment with cholestyramine resulted in greater reductions in TC and

LDL than placebo (TC -17% with cholestyramine vs. -1% with placebo; LDL -26% with cholestyramine vs. -5% with placebo ($p<0.001$).

The National Heart, Lung, and Blood Institute (NHLBI) compared cholestyramine with placebo in 143 patients. Cholestyramine reduced LDL by 26% vs. 5% with placebo ($p<0.001$). There was no significant difference between cholestyramine and placebo in TG or HDL levels.

- *Colesevelam* – One double-blind study compared various doses of colesevelam to placebo for 24 weeks in 494 patients with primary hypercholesterolemia. LDL levels decreased by 18% at the highest dose; all colesevelam doses reduced LDL significantly versus placebo ($p<0.001$). There were small, non-clinically significant increases in HDL and TG.
- *Colestipol* – One large placebo-controlled trial with colestipol published in 1978 reported a 12% reduction in TC; LDL values were not reported.
- *Cholestyramine or colestipol vs. placebo* – In 1972, a study of 45 adults with hyperlipidemia examined the cholesterol lowering activity and safety of colestipol monotherapy or cholestyramine monotherapy versus placebo. After one year of therapy, colestipol and cholestyramine had a similar effect on TC (40% reduction).

ii) Combination therapy with a statin – The BAS are uncommonly used as monotherapy; they are more likely to be used as adjunctive therapy with a statin. Colestipol plus simvastatin (Zocor, generics) has produced LDL reductions of 45-50%. Colesevelam plus simvastatin has resulted in a 48% reduction in LDL.

iii) Clinical outcomes – The only BAS trial that evaluated clinical outcomes was the LRC-CPPT with cholestyramine. This trial reported a 19% reduction in the combined rate of CHD death plus nonfatal MI with cholestyramine vs. placebo (7% vs. 95, respectively; $p<0.05$).

iv) Efficacy conclusion – Treatment with a BAS reduces LDL by15-30%. Use of BAS as monotherapy has declined in popularity, since statins offer greater LDL reduction. Based on indirect comparison of placebo-controlled trials, cholestyramine, colestipol, and colesevelam have comparable efficacy in lowering LDL. There are no direct comparative trials. There is clinical evidence supporting the use of cholestyramine for reducing the risk of cardiovascular events; no such benefit has been documented with colestipol or colesevelam.

3) 3) Safety / Tolerability

a) Fibric Acid Derivatives

i) Myopathy with statin combination therapy

- *Background* – An increased risk of myositis and potentially fatal rhabdomyolysis has been reported with fibric acid derivatives, either as monotherapy or in combination with a statin (particularly cerivastatin); it

appears to be dose-related. This risk was first identified via spontaneous reports to the FDA Adverse Event Reporting System (AERS).

- *Gemfibrozil vs. fenofibrate* – Mechanistically, differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity. Gemfibrozil undergoes glucuronidation metabolism through the uridine diphosphate glucuronosyl transferase (UGT) 1A1 and 1A3 pathways, which results in competition with the statins. Fenofibrate is eliminated via UGT 1A9 and 2B7 pathways, which do not appear to interfere with statin glucuronidation.
- *FDA retrospective review* – A retrospective data analysis of the FDA AERS database found that half of the cases of statin-induced rhabdomyolysis identified were associated with concomitant medications affecting statin metabolism, and of these more than one third were associated with fibric acid derivatives, gemfibrozil in particular. Many of these reports involved cerivastatin, which has now been withdrawn from the market.

  Another study evaluating the FDA AERS database analyzed the reporting rate (not incidence rate) of myotoxicity between fenofibrate plus a statin vs. gemfibrozil plus a statin. Based on 606 adverse event reports compiled from 1998 to 2002, the reporting rate (rhabdomyolysis cases per million U.S. prescriptions) was 0.58 for fenofibrate and 8.6 with gemfibrozil. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship.
- *Fenofibrate/statin combination trial* – In 2005, one randomized, double-blinded 18-week trial (n=600) evaluated safety of monotherapy with low-dose simvastatin (20 mg) versus combination therapy with a standard dose of fenofibrate plus simvastatin 20 mg. The incidence of myalgia in the combination group was 2.2% vs. 2.4% with simvastatin. There were no reports of rhabdomyolysis.
- *Clinical practice guidelines* – Professional organizations have not favored one fibric acid derivative over the other with respect to safety of use in combination with statins. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

ii) Minor adverse effects

- *Lab abnormalities* – Both gemfibrozil and fenofibrate have been associated with abnormal liver function tests when administered as monotherapy. Increases in serum creatinine ranging from 8 to 18% have

been reported with fenofibrate in patients with normal or impaired renal function. Product labeling advises monitoring of serum creatinine during therapy with either fenofibrate or gemfibrozil.

- *Gemfibrozil vs. fenofibrate: minor adverse effects* – Gastrointestinal (GI) complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. The head-to-head efficacy trial mentioned earlier (conducted in 21 patients) did not report adverse events.
- *Fenofibrate formulations: minor adverse effects* – There are no head-to-head trials assessing differences in adverse effects among the newer fenofibrate formulations. Differences in fenofibrate formulations are primarily related to decreases in particle size designed to address bioavailability issues, allowing the most recent products (Tricor, Antara, and Triglide) to offer once daily dosing and be taken without regard to meals. These differences do not appear to equate to differences in GI adverse effects, although comparative data are not available.

iii) Special populations – None of the fibric acid derivatives are FDA-approved for use in pediatric patients. All are rated Pregnancy Category C. Dosage adjustments for both gemfibrozil and fenofibrate are required in patients with mild renal impairment.

iv) Drug interactions –There appear to be no major clinical differences between the products with respect to drug interactions with products other than statins, which were discussed previously.

v) Safety conclusion – There are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

GI complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. There are no comparative data. There are no clinically significant differences between gemfibrozil and fenofibrate with regard to use in special populations or drug interaction potential.

b) Omacor

i) Minor adverse events – Omacor appears to be safe and well tolerated, with GI disturbances reported most commonly. Patients frequently complain of fishy-smelling breath and taste perversion, which may limit compliance.

ii) Special populations – Safety of Omacor has not been evaluated in pediatric patients or pregnant patients. No dosage adjustments are required in renal or hepatic impairment.

iii) Drug-drug interactions – Patients receiving Omacor and anticoagulants require periodic monitoring, due to the potential risk of increased bleeding. Clinically significant drug interactions due to inhibition of CYP450 metabolism are not expected with Omacor.

c) Bile Acid Sequestrants

i) Systemic adverse events – The BAS are not absorbed, thus are associated with a low incidence of systemic effects. Non-GI effects (such as angina and tachycardia, or rash) are rare.

ii) GI adverse events – Constipation is the most common minor adverse effect with all the BAS, occurring with an incidence of greater than 10%. In the LRC-CPPT trial, the incidence of constipation with cholestyramine was 39% vs. 10% with placebo; however, GI distress from cholestyramine appeared to decrease with time. Constipation appears to occur less frequently with colesevelam than with other BAS, based on pooled data in product labeling. Rare reports of GI obstruction, including two deaths, have been reported in pediatric patients receiving cholestyramine.

Chronic use of BAS can cause bleeding due to hypoprothrombinemia secondary to malabsorption of vitamin K.

iii) Drug-drug interactions – Drug interactions with BAS are primarily due to effects on absorption of concomitant oral medications.

iii) Special populations

Pediatrics – Cholestyramine is the only BAS that is FDA-indicated to treat hypercholesterolemia in the pediatric population.

Pregnancy – Cholestyramine and colestipol have a Pregnancy Category C rating; colesevelam has a Category B rating. Because statins are rated Pregnancy Category X, NCEP guidelines state that BAS are recommended for women with elevated cholesterol who are considering pregnancy.

4) Other Factors

a) Fibric Acid Derivatives – Gemfibrozil is given twice daily before meals, while the newer formulations of fenofibrate ((Tricor, Triglide, Antara) may be given once daily without regard to meals.

b) Omega-3 Fatty Acids – Since Omacor has undergone the new drug approval process, the ratio and amount of DHA and EPA contained in each capsule and the amount of other ingredients is known. The FDA has more authority to oversee manufacturing of Omacor than fish oil supplements. Fish oil supplement manufacturers are not required to list ingredients other than omega-3 fatty acids (e.g., omega-6 fatty acids, cholesterol) in their label. The

Omacor formulation requires four capsules daily; higher capsule burdens are necessary with some fish oil supplements.

c) Bile Acid Sequestrants – Cholestyramine is only available in a powder form, which some patients find unpalatable. Cholestyramine and colestipol are available as powders or granules for oral suspension, with colestipol also available in tablet form. Both colestipol and colesevelam require large daily tablet burdens (up to sixteen tablets per day for colestipol and seven for colesevelam).

5) Place in Therapy

a) Fibric Acid Derivatives – Fibric acid derivatives have been used clinically since the 1970s and are effective at lowering TG levels and raising HDL. They are widely used as adjunctive treatment with statins, which primarily reduce LDL.

b) Prescription Omega-3 Fatty Acids (Omacor) – Omacor provides an alternative for patients with elevated TG who are not candidates for niacin or fibric acid derivatives. The American Heart Association (AHA) recommends niacin as first-line for elevated TG. The AHA recommends consumption of a variety of fish as primary prevention, with omega-3 fatty acids potentially considered for secondary prevention. NCEP guidelines recommend either fibric acid derivatives or niacin as first line for elevated TG, along with a high dietary intake of fatty fish or omega-3-containing vegetable oils.

c) Bile Acid Sequestrants – NCEP guidelines recommend BAS for LDL-lowering in patients with moderately elevated LDL; women who are considering pregnancy and have elevated LDL; and patients who need only modest reductions in their LDL to reach their target goal.

6) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) Fibric Acid Derivatives

i) Both gemfibrozil and fenofibrate reduce TG by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

ii) Two placebo-controlled trials with gemfibrozil have shown a benefit in reduction of cardiovascular events in a primary prevention setting and a reduction in nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI (p=0.01) and coronary revascularization (p=0.035).

iii) Although GI adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data

from product labeling. Gemfibrozil must be taken twice daily prior to meals.

iv) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

v) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

vi) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

b) Omega-3 Fatty Acids

i) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers

increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

ii) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG.

iii) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

iv) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

c) Bile Acid Sequestrants

i) The BAS agents reduce LDL by 15-30%. This subclass has largely been replaced by the statins, which decrease LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL. Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

ii) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

iii) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

iv) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. B. LIP-2s – Relative Cost Effectiveness

In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the agents within the fibric acid derivative and BAS subclasses differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of hypertriglyceridemia and hyperlipidemia, respectively. As a result, cost minimization analyses (CMAs) were performed to compare the relative cost effectiveness of the agents within the fibric acid derivative and BAS subclasses. Since Omacor is the only prescription omega-3 fatty acid product, a cost effectiveness analysis (CEA) was conducted to compare it to other agents used in the treatment of hypertriglyceridemia.

Results from the fibric acid derivative CMA revealed: 1) gemfibrozil was the most cost-effective fibric acid derivative, and 2) IDD-P fenofibrate (Triglide) was by far the most cost effective fenofibrate. Among the bile acid sequestrants, the CMA showed that colesevelam was not cost-effective in the treatment of hyperlipidemia when compared to other available agents. The results for the prescription omega-3 fatty acids CEA showed that Omacor was not cost effective in the treatment of hypertriglyceridemia when compared to gemfibrozil, fenofibrate, and niacin. At this time, there is insufficient evidence to support a clinical benefit for omega-3 fatty acids in prevention of CHD. For this reason, the cost effectiveness of Omacor was not evaluated for this consequence or clinical outcome.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various UF scenarios for the LIP-2s was conducted. The goal of the BIA was to aid the Committee in determining which group of LIP-2s best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that maintained fenofibrate (Lofibra), IDD-P fenofibrate (Triglide), cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the relative CEA of the LIP-2 class.

C. LIP-2s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate (Lofibra, generics), IDD-P fenofibrate (Triglide), cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and prescription omega-3 fatty acids (Omacor) be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." The objective is to maximize use of IDD-P fenofibrate (Triglide) in the retail network and mail order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate (Triglide) will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena

D. LIP-2s – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and omega-3 fatty acids (Omacor):

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that some circumstances under which criterion #2 might be considered to apply may be 1) Omacor for patients who cannot take statins or fibric acid derivatives due to a history of myopathy and who cannot tolerate niacin, or 2) colesevelam for patients with a history of GI obstruction or pregnant patients who require treatment with a bile acid sequestrant.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. LIP-2s – UF Implementation Period

Given the relatively low number of beneficiaries are affected (approximately 83,612 patients (65%) of approximately 127,901 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, or prescription omega-3 fatty acids (Omacor) on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary LIP-2 agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day

implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. LIP-2s – BCF Review and Recommendation

Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class.

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs) available in the U.S. The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). These two agents have been marketed for a number of years; finasteride is available generically. The class review did not include the lower dosage (1 mg) strength of finasteride, which is marketed for alopecia (hair loss) under the brand name Propecia, since this indication is not covered by TRICARE.

The 5-ARI drug class accounted for $31.2 million in the MHS expenditures for the period October 2005 to September 2006 and is ranked #50 in terms of total expenditures during that time period. More than 281,000 prescriptions for 5-ARIs were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Pharmacologically, the 5-ARIs reduce prostate volume by inhibiting the conversion of testosterone to dihydrotestosterone (DHT). Finasteride selectively inhibits type I 5-alpha receptors, while dutasteride inhibits both type I and type II receptors; the clinical significance of this difference is unknown. 5-ARIs are used for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Their effect on lower urinary tract symptoms (LUTS) associated with BPH (e.g., urinary frequency, urgency, nocturia, decreased / intermittent force of stream, and the sensation of incomplete bladder emptying) is related to relief of urethral obstruction and may take several months of treatment to become clinically evident. BPH to the point of prostatic obstruction can cause acute urinary retention (AUR), which is considered a medical emergency.

Standard treatments for BPH include watchful waiting (in men with mild symptomatic BPH); alpha blockers (which rapidly relieve symptoms by relaxing prostate and bladder smooth muscle but do not affect prostate volume); 5-ARIs (reduce prostate volume); combination alpha blocker/5-ARI treatment (in men with moderate-to-severe symptomatic BPH); and surgery (in men with severe symptomatic BPH).

A. 5-ARIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the 5-ARI agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does

not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) FDA-approved indications

   Both finasteride and dutasteride are indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of AUR, and reduce the risk of the need for BPH-related surgery. Finasteride is approved for combination therapy with the alpha blocker doxazosin to reduce the risk of symptomatic progression of BPH; labeling for dutasteride does not include an indication for combination therapy. Both are dosed once daily without regard to meals.

2) Efficacy Measures

   The primary outcome measures used to assess efficacy of the 5-ARIs are changes in symptom scores (AUA-SI or IPSS), urinary flow rate (Qmax), reductions in total prostate volume (TPV), and decreased risk of AUR or BPH-related surgery. In trials, a decrease in symptom score of three or more points is generally considered clinically significant; although men rate themselves as slightly improved with a decrease of one to two points. A change in the urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) Efficacy

   a) *Long term placebo-controlled trials* – The most extensive data supporting long term efficacy and safety of the 5-ARIs are from two large randomized, double-blind, placebo-controlled trials. The four-year Proscar Long-Term Efficacy and Safety Study (PLESS) [McConnell et al, 1998] showed a significant reduction in symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo. Data for dutasteride come from pooled analyses of three identical parallel-group trials (ARIA 3001, 3002, 3003) [Roehrborn et al, 2002]. All three trials had a two-year double-blinded phase comparing dutasteride to placebo, followed by a two-year open-label extension phase during which all patients were treated with dutasteride. At the end of the two-year double-blind phase, dutasteride significantly reduced symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo.

      Reductions in the risk of AUR and BPH-related surgery appeared similar. The calculated risk reduction after two years with finasteride (PLESS) was a 57% reduction in AUR (95% CI 40-69%) and a 58% reduction in BPH-related surgery 58% (95% CI 41-65%), compared with placebo. For dutasteride, the risk reduction after two years (ARIA pooled data) was 57% for AUR (95% CI 38-71%) and 48% for BPH-related surgery (95% CI 26-63%), compared with placebo.

   b) *Systematic reviews and meta-analysis* – Two systematic reviews [Clifford et al, 2000; Edwards et al, 2002] and one meta-analysis [AUA Guideline, 2003] concluded that finasteride offers consistent improvement in terms of symptom

relief, urinary flow rate, and decreased risk of AUR and the need for prostatic surgery, compared to placebo. No systematic reviews or meta-analyses are available for dutasteride.

Head-to-head trials – The only fully published head-to-head trial [Clark et al, 2004] compared effects of finasteride and dutasteride on DHT, testosterone, and leutinizing hormone (LH) levels. This 24-week, Phase II, double-blind, placebo-controlled, dose-ranging trial randomized 399 men with BPH to dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg finasteride, or placebo. The mean percent decrease in DHT with dutasteride was more profound and less variable than with finasteride [dutasteride 0.5 mg (the labeled dose) 94.7 ± 3.3% vs. finasteride 5 mg 70.8 ± 18.3%]. Mean testosterone levels increased but remained in the normal range for all treatment groups. Whether or not differences between finasteride and dutasteride with respect to DHT suppression result in a clinically significant difference in patient outcomes has yet to be determined. Limitations of this trial include its short duration relative to the typical onset of benefits from 5-ARIs and its small sample size, especially given that only one of the dutasteride arms was at the labeled dose (0.5mg).

Unpublished summary data from a second head-to-head trial, the Enlarged Prostate International Comparator Study (EPICS), were furnished by the manufacturer of dutasteride [data on file, GlaxoSmithKline]. EPICS compared dutasteride 0.5 mg and finasteride 5 mg in men with BPH. Following a 4-week placebo run-in period, 1630 men were randomized to dutasteride (n=813) or finasteride (n=817) for twelve months. After one year similar improvements from baseline were seen with dutasteride vs. finasteride, respectively, with respect to changes in symptom scores (-5.8 vs.- 5.5), reductions in TPV (-26.3% vs. -26.7%) and Qmax (2.0 vs. 1.7 mL/sec). No statistically significant differences in outcome measures between treatment groups were reported.

c) *Combination therapy trials* – Three short-term combination trials (finasteride plus an alpha blocker) demonstrated no additional benefit compared to alpha blockers alone. However, the large, long-term Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated improvements in LUTS and a greater reduction in overall disease progression (including reduced risk of AUR and need for BPH-related surgery) with combination therapy (finasteride plus doxazosin) versus monotherapy with either agent. The AUA meta-analysis of finasteride trials reported improved AUA-SI scores and Qmax with combination therapy and supported its use in men with LUTS and demonstrable prostate enlargement. There are no published long-term combination trials with dutasteride; therefore, there is insufficient evidence to compare finasteride to dutasteride when used in combination with an alpha blocker.

d) *Prostate cancer* – There is limited evidence concerning the potential use of 5-ARIs for prostate cancer prevention. The only large, long-term trial [Thompson et al, 2003] reported a 24.8% reduction in the prevalence of

prostate cancer in patients receiving finasteride vs. placebo; however, a higher percentage of high-grade prostate cancer tumors was reported with finasteride, compared to placebo. It is not known whether or not dutasteride produces the same effect.

e) Efficacy conclusion – There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery. Summary results from an unpublished head-to-head trial (the Enlarged Prostate International Comparator Study – EPICS) showed similar improvements in symptom scores, TPV, and Qmax; no statistically significant differences in outcome measures were reported. There is insufficient evidence to compare the two agents for use in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial – MTOPS); there are no published long-term combination trials with dutasteride. The clinical significance of more profound suppression of DHT with dutasteride than with finasteride is unknown. The overall effect of 5-ARIs on prostate cancer prevention is unclear.

4) Safety and Tolerability

a) Serious adverse events – There have been no notable reports of serious adverse events with either agent.

b) Overall adverse events – The most common adverse effects are related to sexual dysfunction. Similar incidences of sexual adverse events and gynecomastia have been reported with finasteride and dutasteride. In general, clinical trials report rates of decreased libido of 2 to10%, erectile dysfunction 3 to16%, ejaculatory disorders 0 to 8%, and gynecomastia 1 to 2%. The incidence of sexual dysfunction is generally higher during the first six to twelve months of treatment and diminishes with chronic dosing.

c) Withdrawals due to adverse events during clinical trials – With the exception of gynecomastia, adverse effects are generally not severe enough to discontinue use of 5-ARIs. There do not appear to be major differences between the two agents with respect to withdrawal rates due to adverse events. Reported withdrawal rates in clinical trials of finasteride and dutasteride were low overall, similar in the first year of therapy, and decreased further for both agents during continued treatment.

d) Drug interactions – No major comparative disadvantage was noted for either agent based on its potential for drug-drug interactions. Both are metabolized via the cytochrome P450 (CYP) 3A4 enzyme system and should be used cautiously in patients taking potent CYP 3A4 inhibitors.

e) Special populations – There are no major differences between finasteride and dutasteride with regard to use in special populations; both are pregnancy category X, contraindicated in children and women, and carry warnings regarding exposure to 5-ARIs of women who are pregnant or may become pregnant, due to the potential risk of transdermal absorption and fetal exposure (feminization of male fetuses is an expected consequence of the inhibition of the conversion of testosterone to DHT by 5-ARIs). Men taking a 5-ARI should defer blood donation for six months from discontinuation of therapy to avoid possible administration of the drug to a pregnant female transfusion recipient. Neither finasteride nor dutasteride requires dosing adjustments or has special dosing requirements, although caution is advised in hepatic dysfunction.

f) Other factors – 5-ARIs as a class are associated with a decrease in prostate specific antigen (PSA) concentrations of about 50% after six months of treatment. Neither drug appears to interfere with detection of prostate cancer when PSA values used for prostate cancer screening are appropriately adjusted (they should be doubled in men who have received 5-ARI therapy for at least six months).

g) Safety and tolerability conclusion – There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated; with the most common adverse effects related to sexual dysfunction and diminishing with chronic dosing. Reported withdrawal rates due to adverse effects are low overall in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment. The two agents appear similar with regard to potential drug interactions and use in special populations (both are contraindicated in women and children and carry special warnings against exposure of women who are or may become pregnant). Neither agent appears to interfere with the prostate cancer detection.

5) Therapeutic Interchangeability

Finasteride and dutasteride appear similar in terms of efficacy, safety, and tolerability, and are used in the same patient population. Neither drug offers a unique benefit, nor is it likely that a patient who did not have an adequate response with one 5-ARI would have a better response with the other. Either finasteride or dutasteride could be expected to meet the needs of the majority of DoD BPH patients.

6) 5-ARIs – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume,

increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery.

b) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum DHT levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (EPICS) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.

c) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (MTOPS); there are no published long-term combination trials with dutasteride.

d) The overall effect of 5-ARIs on prostate cancer prevention is unclear.

e) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.

f) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.

g) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.

h) Neither agent appears to interfere with prostate cancer detection.

i) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. 5-ARIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the 5-ARIs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the 5-ARI medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, several CMAs were performed to compare the relative cost effectiveness of the 5-ARIs by condition set. The CMAs compared the weighted average cost per day of treatment

for each drug product across all three points of service. In addition, a CEA was conducted evaluating the cost per BPH surgery avoided for each of the 5-ARIs.

Results from the CMAs showed that finasteride was the most cost effective agent with a lower cost per day of treatment than dutasteride across all conditions sets evaluated. In addition, finasteride was the preferred choice in the CEA with a lower expected cost per BPH surgery averted than dutasteride.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of 5-ARIs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) to accept the 5-ARI relative CEA as presented by the PEC.

C. 5-ARI – UF Recommendations

COMMITTEE ACTION*:* In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that finasteride be maintained as formulary on the UF and that dutasteride be classified as non-formulary under the UF.

D. 5-ARI – MN Criteria

Based on the clinical evaluation for dutasteride, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for dutasteride:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. 5-ARI – UF Implementation Period

Because of the relatively few number of beneficiaries affected (approximately 20,917 patients (41%) of approximately 51,017 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have dutasteride on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary 5-ARI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. 5-ARIs – BCF Review and Recommendations

Currently there are no 5-ARI agents on the BCF. The P&T Committee had previously determined at the November 2006 meeting that at least one 5-ARI would be placed on the BCF. Finasteride is widely used at MTFs, has clinical data supporting efficacy for decrease in total prostate volume, increase in urinary flow rate, and improvement in symptoms, reductions in risk of acute urinary retention and BPH-related surgery. Finasteride is clinically similar to dutasteride with respect to safety and tolerability, and is the most cost effective 5-ARI. The P&T Committee agreed that finasteride should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend adding finasteride as the BCF selection in this class.

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/ sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting. The PPI class was previously reviewed by the P&T Committee in February 2005.

As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class is now #1 in terms of MHS expenditures: more than $485 million over the 12 months from April 06 to March 07, compared to about $350 million in FY 2005. MTF pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TMOP. Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Pharmacologically, PPIs suppress the final step in gastric acid production. They have become the standard of care for treatment of acid-related disorders, particularly treatment of erosive or ulcerative disease.

Standard practice in the initial management of dyspepsia or gastroesophageal reflux disease (GERD) indicates that if certain "alarm features" (i.e., signs of potential underlying cancer such as melena, persistent vomiting, dysphagia, hematemesis, anemia, or involuntary weight loss) are not present, patients should be treated with an empiric trial of 4 to 8 weeks of PPI therapy. In populations where the prevalence of *H. pylori* is greater than 10%, *H. pylori* testing should occur prior to further evaluation, with subsequent treatment if positive. Patients with inadequate symptom relief after 8 weeks should receive endoscopy and further management based on endoscopy results. GERD is often a relapsing-remitting disease which requires long-term medical maintenance therapy; in many cases PPIs will be continued for an extended period of time.

A. PPIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the PPIs currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) FDA-Approved Indications and Other Uses

All of the PPIs are FDA-approved for the treatment of erosive esophagitis (EE) and maintenance of healed EE. All PPIs except pantoprazole have at least one indication for ulcer treatment (e.g., duodenal or gastric ulcers and/or ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) or caused by *H. pylori*). All PPIs except pantoprazole and omeprazole/sodium bicarbonate have an FDA indication as part of a multi-drug regimen for the eradication of *H. pylori*. All PPIs except omeprazole/sodium bicarbonate have an indication for the treatment of hypersecretory conditions such as Zollinger-Ellison.

In practice, most of the agents have published data showing effectiveness for use in any of the acid related disorders, and are commonly prescribed to treat all acid related conditions, regardless of FDA indication. Omeprazole, lansoprazole, and esomeprazole are indicated for use in children.

PPIs are also being studied and used outside the area of acid-related disorders (e.g., for surgical procedure prophylaxis, posterior laryngitis, and chronic cough). More data are needed to support broader use of PPIs for these conditions.

2) Efficacy Measures

Comparative efficacy was evaluated on a disease state basis based on FDA indicated uses of the PPIs. The emphasis was on objective clinical endpoints (ulcer healing, esophagitis healing, maintenance of healing / prevention of disease, and symptomatic resolution) rather than surrogate endpoints (such as pH

measurements, supplemental antacid use and serum drug levels), given the uncertain relationship of surrogate endpoints to clinical outcomes.

3) Clinical Evidence

The review focused primarily on randomized, double-blinded trials where one PPI was compared to another (head-to-head or direct comparison trials), or to another active comparator such as histamine-2 receptor antagonists (e.g., ranitidine, cimetidine, etc). Three good quality systematic reviews summarized the available data, supplemented by more recently published trials. The systematic reviews included PPI reviews from the Oregon Health and Science University's Drug Effectiveness Review Project (DERP; July 2006) and the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS; Aug 2005), and the Agency for Healthcare Research and Quality (AHRQ) 2005 Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease guideline.

It should be noted that no published outcomes evidence is available for either omeprazole magnesium (Prilosec OTC) or the immediate release/sodium bicarbonate (Zegerid) formulations of omeprazole. FDA approval of these formulations relied on the original omeprazole data.

4) Efficacy

a) EE healing

Evidence from head-to-head trials suggests the majority of patients obtain complete healing of erosive disease within eight weeks of treatment on any PPI, with most patients achieving symptom relief within four weeks of initiating treatment.

Of the 25 head-to-head trials published in the clinical literature, only six showed a statistically significant difference in healing rates among the PPIs. One of these predictably found omeprazole 20 mg to be more efficacious than lansoprazole 15 mg, but similar to lansoprazole 30 mg, which is the dose typically used for EE healing.

Two trials comparing esomeprazole and lansoprazole reported differences favoring esomeprazole, with one trial reporting statistically significant differences in healing and symptom resolution at four weeks that disappeared by 8 weeks and the other reporting a small but statistically significant difference in healing and symptom resolution at four weeks and healing at eight weeks. Another head-to-head trial of esomeprazole and lansoprazole showed no significant difference in healing or symptom resolution at the same time points.

Two trials comparing esomeprazole and omeprazole reported differences favoring esomeprazole; both trials compared esomeprazole 40 mg to omeprazole 20 mg, which are not equivalent doses. Two adequately powered later trials, one comparing esomeprazole 40 mg to omeprazole 20 mg and one comparing esomeprazole 20 mg to omeprazole 20 mg, failed to show

statistically significant differences in healing rates at four and eight weeks or symptom resolution at 4 weeks.

One trial comparing esomeprazole to pantoprazole reported differences favoring esomeprazole; this trial appears to have some internal validity issues. Another trial comparing esomeprazole 40 mg and pantoprazole 40 mg failed to find any statistically significant differences in healing or symptom relief.

Conclusion – Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

b) Maintenance of healing in erosive esophagitis

The evidence includes six clinical trials comparing various PPIs, along with a placebo-controlled rabeprazole trial and a comparison of pantoprazole and ranitidine. There are substantial methodological differences among trials (e.g., methods of evaluating healing, duration, study populations, and comparators used), as well as internal validity issues and small trial sizes that make it impossible to draw conclusions regarding the superiority of one agent over another.

Conclusion – There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to others for maintenance of EE healing.

c) Ulcer healing and maintenance of healing

Fifteen head-to-head trials compared efficacy of various PPIs to omeprazole for initial healing and/or maintenance of healing in duodenal, gastric, and NSAID-induced ulcers. No statistically significant differences were found for any comparators versus omeprazole for primary endpoints of ulcer healing and maintenance of healing or for measures of symptom resolution and improvement.

Conclusion – There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease (PUD) and/or NSAID-induced ulcers.

d) Endoscopy negative reflux disease (ENRD)

ENRD is an incompletely understood variant of GERD. It is estimated that as many as half of patients diagnosed with GERD may fall into this category; however, there are few clinical trials specifically focusing on ENRD. Patients with ENRD are generally considered more difficult to treat than patients with positive findings on endoscopy.

Six trials show efficacy of various healing or maintenance doses of PPIs for initial resolution of heartburn (the primary outcome in all of the trials). Three other trials compare on-demand use of a PPI to placebo or an active

comparator (e.g., a histamine-2 blocker) as continuation therapy after initial resolution of symptoms.

Conclusion – Based on available clinical trials, PPIs appear to be similarly efficacious as short-term treatment for ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

e) H. pylori eradication with multi-drug regimens

There are at least 39 head-to-head trials comparing all of the PPIs in various multi-drug combination regimens with antibiotics. Substantial differences among studies in doses of PPIs and antibiotics, duration of treatment, methods of assessing *H. pylori* eradication, and patient populations make comparisons across studies difficult. A good quality meta-analysis (2003) using omeprazole as the reference for comparison found no difference in eradication rates among PPIs; earlier systematic reviews (1998, 1999) came to similar conclusions.

Conclusion – H. pylori eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

f) Efficacy in Pediatric Patients

Omeprazole, lansoprazole and esomeprazole have indications for treatment of symptomatic GERD in pediatric patients, while omeprazole and lansoprazole have indications for treatment and maintenance of healing of EE. Comparisons of PPIs across trials is difficult; most trials in pediatric patients were small, some were open-label or non-controlled, and surrogate endpoints used to assess symptom resolution varied widely. There was no evidence to support greater efficacy for any one PPI compared to others.

Conclusion – There are insufficient data to suggest superiority of one PPI over others for treatment of pediatric patients. Pantoprazole and rabeprazole do not have an FDA-approved pediatric indication.

5) Safety/Tolerability

a) *Serious adverse events* – A long-standing potential safety concern with PPIs is prolonged hypergastrinemia, which can lead to hyperplasia of both normal and neoplastic enterochromaffin-like cells in the GI tract, potentially leading to cancer. However, the precise role of achlorhydria-induced increases in gastrin expression in gastrointestinal carcinogenesis is unknown. Risk of atrophic gastritis and gastric bacterial overgrowth is increased with long-term PPI use, although the clinical significance is unclear.

PPIs have been associated with *C. difficile* infection, especially in patients taking concomitant antibiotics; caution is particularly indicated with *H. pylori* eradication regimens.

Acute interstitial nephritis has been rarely reported with PPIs. In addition, epidemiological data have suggested an association between PPIs and increased risk of fracture; potential study limitations are numerous, and no definitive evidence is available.

b) *Overall adverse events and withdrawal due to adverse events* – In general, adverse effects are similar to placebo, with an overall incidence rate of less than 5%. Most commonly reported are headache, diarrhea, abdominal pain, and nausea. Head-to-head trials have shown no differences in short-term tolerability; withdrawal rates due to adverse events are very low. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials.

c) *Drug interactions* – PPIs have the potential for causing drug interactions based on several mechanisms, including CYP450 inhibition, effects on the P-glycoprotein membrane transport system in columnar cells of the small intestine, and changes in gastric pH, which can affect absorption of other medications. Omeprazole and esomeprazole may have the most potential for CYP450 drug interactions. Increased effects of warfarin have been reported most frequently with omeprazole, lansoprazole, or pantoprazole, although this is a potential interaction for all PPIs. Most drug interactions are minor in nature.

d) *Special populations* – Dosage adjustments for all PPIs, except pantoprazole, should be considered in patients with severe hepatic disease. None of the PPIs require adjustment in patients with chronic renal insufficiency, elderly patients, or based on gender or race. Omeprazole is classified as Pregnancy Category C; other PPIs are Pregnancy Category B. PPIs are excreted in breast milk and are not recommended for use during breastfeeding.

Zegerid contains 300-460 mg of sodium per tablet due to its sodium bicarbonate component; caution is advised for patients who should avoid consumption of large amounts of sodium.

e) *Other factors* – Lansoprazole, esomeprazole and omeprazole/sodium bicarbonate have dosage forms that can be used in pediatric patients or patients with swallowing difficulties. All three are available as packets for oral suspension; lansoprazole is also available as an orally disintegrating tablet. Omeprazole capsules contain enteric-coated granules commonly used to prepare a bicarbonate-based extemporaneous suspension.

Pantoprazole was the only PPI available in intravenous (IV) form for several years; however, both esomeprazole and lansoprazole have recently developed IV formulations. (It should be noted that due to their route of administration and lack of outpatient use, the IV formulations are not eligible for inclusion on the UF and not included in this review.)

f) *Safety and tolerability conclusion* – The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials. In general, agents appear very similar with respect to safety and tolerability. Minor differences include the lack of a requirement to adjust the dose of pantoprazole in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently

introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

6) PPIs – Overall Clinical Effectiveness Conclusion:

The P&T Committee concluded that:

a) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

b) Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

c) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

d) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in PUD and/or NSAID-induced ulcers.

e) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

f) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

g) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

h) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

i) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. PPIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the PPIs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class.

Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the PPI medications differed in regard to efficacy, safety, tolerability, or clinical outcomes data in the treatment of EE healing and maintenance of healing, ulcer healing and maintenance of healing, *H. pylori* eradication, and ENRD. As a result, several CMAs were performed to compare the relative cost effectiveness of the PPIs by condition set (the seven condition sets are listed below). The CMAs compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service.

1) C7301: Two or fewer PPIs are selected for the UF and one PPI is selected for the BCF. ($\leq$2 UF, 1 BCF)
2) C7302: Three or four PPIs are selected for the UF and one PPI is selected for the BCF. (3-4 UF, 1 BCF)
3) C7303: Three or four PPIs are selected for the UF and two PPIs are selected for the BCF. (3-4 UF, 2 BCF)
4) C7304: Five or more PPIs are selected for the UF and one PPI is selected for the BCF. ($\geq$5 UF, 1 BCF)
5) C7305: Five or more PPIs are selected for the UF and two PPIs are selected for the BCF. ($\geq$5 UF, 2 BCF)
6) C7306: Two PPIs (generic omeprazole and one other PPI) are selected for the UF and generic omeprazole is the only PPI selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole before any other PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.
7) C7307: Two PPIs (generic omeprazole and one other PPI) are selected for the UF. Generic omeprazole will be selected to the BCF and the other PPI may be selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole or the second UF PPI before any third tier PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.

Results from the PPI CMAs showed three important findings: 1) as expected, the more restrictive the UF scenario, the lower the cost per day of treatment; 2) for the three condition sets that evaluated UF scenarios with two or fewer UF agents (C7301, C7306, and C7307), omeprazole and esomeprazole were the most cost effective agents; and 3) for the two condition sets that evaluated UF scenarios with three to four UF agents (C7302 and C7303), omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in

determining which group of PPIs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario (condition set C7307) that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a step therapy PA was the most cost effective scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (14 for, 0 opposed, 0 abstention, and 3 absent) to accept the PPI relative CEA as presented by the PEC.

C. PPIs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the purchased care arena.

D. PPIs – PA Criteria

The P&T Committee agreed that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

3) Automated PA criteria:
    a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
4) PA criteria if automated criteria are not met:
    a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
    b) Treatment with omeprazole or esomeprazole is contraindicated.

The P&T Committee noted that in order for a patient to receive a non-formulary PPI agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate would NOT automatically receive it at the formulary cost-share.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

E. PPIs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. PPIs – UF Implementation Period

Even though a large number of beneficiaries are affected (approximately 453,525 patients [64%] of approximately 702,841 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The P&T Committee believed the considerable cost avoidance associated with this recommendation warranted a more aggressive implementation period. Furthermore, the P&T Committee was anxious to extend the $3.00 cost-share for esomeprazole to beneficiaries as soon as possible. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary PPI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. PPIs – BCF Review and Recommendations

Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class.

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period. Approximately 140,000 30-day equivalent ARB prescriptions are dispensed monthly in both retail network pharmacies and MTFs; approximately 80,000 30-day equivalent ARB prescriptions are dispensed monthly in the TMOP. The most frequently dispensed ARBs in the MHS are valsartan at 50,000 prescriptions per month and valsartan at 40,000 prescriptions per month. However, the angiotensin converting enzyme (ACE) inhibitor lisinopril is still by far the most frequently prescribed ACE inhibitor or ARB in the MHS, with over 150,000 prescriptions dispensed monthly.

A. ARB Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ARBs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

The ARB drug class was previously evaluated for UF status in February 2005. The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure (HF), and type 2 diabetic nephropathy.

Evidence of the ARBs for use in indications other than hypertension is difficult to interpret, due to the lack of head to head trials between the ARBs that assess clinical outcomes. There are no head-to-head trials assessing efficacy of the ARBs compared to ACE inhibitors for reducing cardiovascular outcomes in HF or type 2 diabetic nephropathy.

1) Efficacy

a) Efficacy Measures

The P&T Committee considered evidence of benefit in improving clinical outcomes of greater importance than effects on physiologic endpoints when evaluating relative clinical effectiveness differences among ARBs. Clinical outcomes include all-cause mortality, cardiovascular mortality, hospitalization for HF, stroke, development of end stage renal disease (ESRD), need for dialysis, and need for renal transplant. Examples of physiologic endpoints include reduction in blood pressure (BP), changes in pulmonary capillary wedge pressure, changes in urinary protein excretion rate, reduced rate of decline in glomerular filtration rate (GFR), changes in urinary albumin to creatinine ratio, and changes in urinary albumin excretion rate.

b) Hypertension

All seven ARBs are approved by the FDA for treating hypertension. One meta-analysis evaluating the ARBs (with the exception of olmesartan) examined data from over 51 clinical trials enrolling over 12,000 patients with hypertension. The meta-analysis reported that treatment with any ARB reduced systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure (DBP) by 4.5 to 6.5 mm Hg, compared to placebo (placebo-corrected values). Pooled clinical trial data from seven studies with olmesartan enrolling over 2,600 patients show similar BP reductions to the other six ARBs.

All of the ARBs combinations with HCTZ are approved solely for treatment of hypertension. Joint National Commission (JNC) guidelines for treating hypertension state that many patients will require more than one drug to reach blood pressure goals. Addition of HCTZ to an ARB increases efficacy. Treatment with an ARB as monotherapy results in a 53-63% response rate, based on a goal DBP < 90 mm Hg. The response rate increases to 56-70% with the addition of HCTZ to the ARB.

c) Hypertension and Clinical Outcomes

The ARBs have been evaluated in four large clinical trials to assess efficacy for reducing the risk of cardiovascular events in patients with hypertension. Based on the results of the LIFE trial, losartan is labeled to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH), however the benefit does not apply to Africa Americans. The benefits of losartan were likely due to greater reductions in BP compared to that achieved with the comparator drug, atenolol (Tenormin, generics). JNC guidelines mention that several antihypertensive drugs classes, including ACE inhibitors and diuretics, are associated with regression of LVH. Reducing BP is well-proven as an effective mechanism to reduce stroke risk, regardless of the antihypertensive agent administered.

Candesartan was found to reduce non-fatal stroke in the SCOPE trial in elderly patients when compared to placebo. When valsartan was compared to amlodipine (Norvasc) in the VALUE trial, there were no differences noted in

cardiovascular mortality or all-cause mortality between the two drugs, however, there were fewer MIs, fatal strokes, and nonfatal strokes with amlodipine. The beneficial results with amlodipine were attributed to a greater percentage of patients achieving target BP goals vs. valsartan (64% versus 58%). In the Jikei Heart Study, valsartan was found to reduce cardiovascular events and strokes, compared to placebo, in a Japanese population.

Candesartan and valsartan are not currently labeled to reduce cardiovascular outcomes in hypertensive patients. For all four trials (LIFE, SCOPE, VALUE, Jikei Heart Study), differences in blood pressure reduction largely account for reported differences in cardiovascular outcomes of ARBs versus other antihypertensives.

e) Chronic Heart Failure

There are no head to head trials comparing the ARBs for use in chronic heart HF. Two large, randomized, placebo-controlled trials, one each with valsartan and candesartan, demonstrated a reduction in the risk of hospitalization due to chronic HF, a clinically relevant outcome.

Based on the results of the Val-HeFT trial, the FDA approved valsartan for use in patients with heart failure. In the Val-HeFT trial, valsartan treatment resulted in a significant 4.4% absolute risk reduction in HF hospitalizations, vs. placebo. A significant reduction in the primary composite endpoint (all-cause mortality/HF hospitalization) was also seen. The previous limitation in the package insert that valsartan should be restricted for use only in HF patients intolerant of ACE inhibitors has now been removed.

The CHARM trials with candesartan support its use in chronic HF, and it is FDA-approved for this indication. A 4.3% absolute risk reduction in HF hospitalization occurred with candesartan treatment, compared to placebo. A significant reduction in the composite primary endpoint (cardiovascular mortality/HF hospitalization) was also shown.

For the other ARBs, losartan was not superior to captopril in reducing death and HF hospitalization in the ELITE II trial. Two pilot studies are available with irbesartan and telmisartan that show reduction in pulmonary capillary wedge pressure. No trials assessing use of eprosartan or olmesartan in HF have been published.

The P&T Committee agreed that there was no evidence that either valsartan or candesartan were preferable relative to the other for the treatment of chronic HF. Since none of the other ARBs have an indication for HF or evidence showing a reduction in clinically relevant outcomes related to chronic HF, the P&T Committee agreed that valsartan and candesartan were preferable to the other five ARBs for the treatment of HF.

f) Type 2 Diabetic Nephropathy

Patients with type 2 diabetes frequently progress from microalbuminuria to overt proteinuria, with decreasing GFR and eventual development of ESRD.

However, the most common cause of death in diabetic patients is due to cardiovascular complications.

i) Microalbuminuria

Head-to-head trials – Two abstracts noted no difference between telmisartan vs. losartan, and telmisartan vs. valsartan in reducing the rate of decline of renal function, as measured by change in urinary protein excretion ratio. However, neither study has been published in a peer-reviewed journal.

Placebo- or active-controlled trials – Benefits on physiologic outcomes in patients with microalbuminuria have been shown with candesartan, irbesartan, telmisartan and valsartan in small studies with placebo or active comparators (usually an ACE inhibitor or calcium channel blocker). There is no published data evaluating efficacy of eprosartan or olmesartan in either microalbuminuria or nephropathy.

ii) Nephropathy

Two ARBs have shown efficacy in clinical outcomes for patients with overt nephropathy and type 2 diabetes mellitus. Both irbesartan and losartan are labeled for use in patients with type 2 diabetic nephropathy, based on the results of the IDNT and RENAAL trials, respectively.

Treatment with losartan resulted in a significant 16% relative reduction (3.6% absolute risk reduction) in the primary composite endpoint (risk of doubling of serum creatinine, death, and ESRD, defined as the need for dialysis or renal transplant), compared to placebo. In the IDNT trial, a significant 20% relative reduction (6.4% absolute risk reduction) was seen with irbesartan compared to placebo when the same composite endpoint was evaluated.

The P&T Committee agreed that there was no evidence that either irbesartan or losartan were preferable relative to the other in patients with type 2 diabetic nephropathy. Since none of the other ARBs has an indication for HF or evidence showing a reduction in clinically relevant outcomes related to type 2 diabetic nephropathy, the P&T Committee agreed that irbesartan and losartan were preferable to the other five ARBs for reducing the risk of doubling of serum creatinine, death, and ESRD in type 2 diabetic nephropathy.

g) Post MI

Valsartan has an additional indication for use in clinically stable patients with left ventricular systolic dysfunction (LVSD) following an MI, to reduce the risk of MI. FDA approval was based on the VALIANT trial, where valsartan was compared with the ACE inhibitor captopril (Capoten, generics). There was no significant difference between valsartan and captopril in all-cause mortality or cardiovascular mortality post-MI.

Overall, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than does valsartan. The aldosterone antagonists spironolactone and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

2) Safety / Tolerability

The ACE inhibitors and ARBs have similar safety concerns regarding hyperkalemia, elevations of serum creatinine, angioedema, and pregnancy category labeling. The ARBs have an incidence of cough similar to placebo.

These medications are generally well-tolerated, with adverse event rates for all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum creatinine, and angioedema, does not appear to differ among agents. Drug interaction profiles are similar. All ARBs are rated pregnancy category C during the first trimester, and pregnancy category D during the second and third trimesters, based on the occurrence of fetal abnormalities with ACE inhibitors. The P&T Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability.

3) Other Factors

The P&T Committee agreed that although there were no clinically significant differences in minor factors between the ARBs, including twice daily dosing and availability in bulk bottles.

4) DoD Utilization

A data analysis of ARB prescriptions using the Pharmacy Data Transaction Service (PDTS) was conducted to determine DOD ARB utilization by FDA approved indication. FDA-approved indication was based on presence of other background medications in the pharmacy profile, (e.g., evidence of digoxin, a loop diuretic or aldosterone antagonist for HF; and use of insulin, oral diabetic medication or blood glucose test strips for diabetic nephropathy). A two-day cross section of 11,317 patients receiving an ARB or ARB/HCTZ combination on 30-31 Mar 07 found 59% of MHS patients were using the ARB for hypertension, 28% for diabetes, 21% for HF, and 8% for both HF and diabetes.

5) Therapeutic Interchangeability

For hypertension, there is a high degree of therapeutic interchangeability for all seven ARBs. Candesartan and valsartan have a high degree of therapeutic interchangeability for chronic HF. For type 2 diabetic nephropathy, irbesartan and losartan have a high degree of therapeutic interchangeability.

6) Clinical Coverage

To meet the needs of the majority of patients in DoD, ideally the UF would include availability of one ARB with evidence for treating HF, and one ARB with evidence for treating type 2 diabetic nephropathy. A third ARB is not necessarily required, as all the ARBs are effective for hypertension, regardless of whether they have additional labeled indications.

7) ARB Overall Clinical Effectiveness Conclusion

The DoD P&T Committee concluded that:

a) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

b) Although losartan is labeled to reduce the risk of stroke in patients with LVH, JNC guidelines support use of other antihypertensive drugs (e.g., ACE inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.

c) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing HF hospitalizations in patients with chronic HF.

d) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of ESRD) in patients with type 2 diabetic nephropathy.

e) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with LVSD. However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone are also labeled for use or have shown efficacy in the post-MI setting.

f) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

***COMMITTEE ACTION*:** The P&T Committee voted (15 for, 0 against, 0 abstained, 2 absent) to accept the ARB clinical effectiveness conclusion stated above.

B. ARBs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the ARBs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the ARB medications differed in regards to efficacy, safety, or tolerability in the treatment of hypertension. However, several products did have additional clinical outcomes data and FDA approved indications for the treatment of chronic HF (candesartan and valsartan) and type 2 diabetic nephropathy (losartan and irbesartan). The clinical review determined that a UF scenario with an agent from these two additional subgroups would be clinically advantageous. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents by

condition set (3 or fewer agents on the UF, 4 – 5 agents on the UF, and 6 or more agents on the UF) and by indication (hypertension, chronic HF, and type 2 diabetic nephropathy). The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the ARB CMA showed several important findings: (1) a UF scenario with three or fewer agents on the UF was the most cost effective condition set; (2) telmisartan was the most cost effective agent for the management of hypertension; (3) among agents for the management of chronic HF, candesartan was more cost effective than valsartan when three or fewer agents were included on the UF; and (4) losartan and irbesartan had similar cost effectiveness profiles for the treatment of type 2 diabetic nephropathy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of ARBs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The Committee accepted the conclusions stated above and determined from the BIA that the UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the ARB relative CEA as presented by the PEC.

C. ARBs – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF.

D. ARBs – MN Criteria

Based on the clinical evaluation for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ:

1) Formulary alternatives are contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

4) The patient previously responded to a nonformulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

The P&T Committee specifically noted that some circumstances under which criterion #4 might be considered to apply may be for 1) post-MI patients with previous angioedema or other intolerance to ACE inhibitors, who are stabilized on valsartan or valsartan/HCTZ, or 2) chronic HF patients stabilized on a non-formulary ARB or ARB/HCTZ combination for whom changes in therapy might result in destabilization.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. ARBs – UF Implementation Period

Because of the large number of beneficiaries affected (approximately 228,000 patients (59%) of approximately 387,000 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan, and valsartan/HCTZ on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary ARB agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. ARBs – BCF Review and Recommendation

COMMITTEE ACTION: Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF.

G. Therapeutic Class Reclassification

The Committee agreed that the ARB class should be reclassified and consolidated with other drug classes that affect the renin-angiotensin system. These include ACE inhibitors, ACE/CCB combinations, ARBs, ARB/CCB combinations, and any newly approved antihypertensives affecting the renin-angiotensin system. The new class will be called the Renin-Angiotensin Antihypertensives (RAAs).

10. QUANTITY LIMITS

A. Mometasone nasal spray (Nasonex) – The current QL for mometasone nasal spray is 1 inhaler (17 gm = 120 sprays) per 30 days or 3 inhalers (51 gm) per 90 days. Nasonex, which was previously indicated only for allergic rhinitis at a maximum dose of 2 sprays in each nostril QD (4 sprays per day), received an indication in late 2004 for the treatment of nasal polyps at a maximum dose of 2 sprays in each nostril twice daily (8 sprays per day). TMOP personnel recently reported an increased number of QL override requests for Nasonex, based on dosing consistent with the nasal polyp indication. Accordingly, the P&T Committee recommended an increase in the QL to accommodate the higher maximum dose for nasal polyps.

COMMITTEE ACTION: The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (TRRx), 102 gm (6 inhalers) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

B. **Ipratropium nasal spray 0.03% and 0.06% (Atrovent Nasal Spray) –** The current QL for Atrovent nasal spray is a collective limit (including both strengths) of 30 mL per 30 days or 90 mL per 90 days. The 0.03% strength, supplied in 30 mL bottles containing 345 sprays per bottle, is indicated for perennial rhinitis in divided doses of up to 12 sprays per day. Taking into account initial priming (7 sprays), 30 mL would equal 28 days supply, assuming consistent use at the maximum recommended dose. The 0.06% strength, supplied in 15 mL bottles containing 165 sprays per bottle, has two indications: 1) rhinorrhea associated with the common cold at divided doses of up to 16 sprays per day; and 2) rhinorrhea associated with seasonal allergic rhinitis at divided doses of up to 16 sprays per day. Based on the indication for seasonal allergic rhinitis and taking into account initial priming, 30 mL would equal 20 days supply, assuming consistent use at the maximum recommended dose.

The P&T Committee also reviewed data concerning QL rejections for Atrovent 0.03% and 0.06%, indicating that approximately 7% of prescriptions for either strength (about 300 prescriptions per month at retail network pharmacies and the TMOP) are initially rejected by the PDTS based on QLs. This is consistent with recent reports from TMOP of an increased number of QL override requests for Atrovent nasal spray.

Based on these data and given that seasonal allergic rhinitis can last considerably longer than 3 weeks, the P&T Committee agreed that the QL for the higher 0.06% strength should be increased. The P&T Committee also agreed that the QL for the lower 0.03% strength should be increased, but requested follow-up monitoring to determine if the change in QLs unduly affected utilization patterns, since the majority of patients should need no more than 1 inhaler per 30 days.

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (TRRx), 6 inhalers (180 mL) per 90 days (TMOP); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45

mL) per 30 days (TRRx), 9 inhalers (135 mL) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents under the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and that the drug had not been excluded from the UF based on clinical issues alone.

2) The non-formulary agent becomes generically available and:
   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system
   b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.
3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:
   a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
   b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. F or example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

12. CLASS OVERVIEWS

Class overviews for the newer antihistamines, targeted immunomodulatory biologics, leukotriene modifiers, beta/alpha-beta blockers, and alpha blockers for BPH were presented to the P&T Committee. Preliminary information for the technical review for the blood glucose test strips was also presented.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the August 2007 or November 2007 meetings; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 16 May 2007. The next meeting will be August 14-15, 2007.

_____signed_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	Pending approval	Pending approval
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	Pending approval	Pending approval
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	Pending approval	Pending approval
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	Pending approval	Pending approval
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			Pending approval	Pending approval
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. May 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Lapatinib tablets (Tykerb, Glaxo) tyrosine kinase inhibitor	Mar 07 ▪ In combination with capecitabine for treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2, and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 250 mg: 225 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 250 mg: 150 tabs per 30 days
Vorinostat capsules (Zolinza; Merck) histone deactylase inhibitor	Oct 06 ▪ Treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 100 mg: 180 caps per 45 days ▪ Retail Network o Days supply limit 30 days o 100 mg: 120 caps per 30 days
Arformoterol inhalation solution (Brovana; Sepracor) inhaled long-acting beta agonist	Oct 06 (launched Apr 07) ▪ Long term twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. For use by nebulization only.	No UF recommendation at this meeting. Consideration of UF status deferred until inhaled long-acting beta agonists are reviewed; UF review anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o 180 unit dose 15 mcg/2 mL vials per 90 days ▪ Retail Network o 60 unit dose 15 mcg/2 mL vials per 30 days

Appendix C – Table 3. Table of Abbreviations

5-ARI	5-alpha reductase inhibitor
ACE	angiotensin converting enzyme
AERS	adverse event reporting system
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
AUA	American Urological Association
AUA-SI	American Urological Association symptom index
AUR	acute urinary retention
BAP	Beneficiary Advisory Panel
BAS	bile acid sequestrant
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
BP	blood pressure
BPH	benign prostatic hyperplasia
CAD	coronary artery disease
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CMA	cost minimization analysis
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CPAP	continuous positive airway pressure
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DHA	docosahexaenoic acid
DHT	dihydrotestosterone
DoD	Department of Defense
DBP	diastolic blood pressure
EE	erosive esophagitis
ENRD	endoscopy-negative reflux disease
EPA	eicosapentaenoic acid
EPICS	Enlarged Prostate International Comparator Study
ESRD	end stage renal disease
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes trial
FY	fiscal year
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione
GFT	glomerular filtration rate
HCTZ	hydrochlorothiazide
HDL	high density lipoprotein
HF	heart failure
HHS	Helsinki Heart Study
IDD-P	Insoluble drug delivery microparticle
IPSS	International Prostate Symptom Score
IV	intravenous

Appendix C – Table 3. Table of Abbreviations (continued)

JNC	Joint National Council
LDL	low density lipoprotein
LH	leutinizing hormone
LIP-2	Antilipidemics II
LRC-CPPT	Lipid Research Clinics – Coronary Primary Prevention Trial
LUTS	lower urinary tract symptoms
LVH	left ventricular hypertrophy
LVSD	left ventricular systolic dysfunction
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	military treatment facility
MTOPS	Medical Therapy of Prostatic Symptoms
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
PPI	proton pump inhibitor
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PSA	prostate specific antigen
PUD	peptic ulcer disease
QD	once daily
Qmax	urinary flow rate
RAAs	renin-angiotensin antihypertensives
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPV	total prostate volume
TRRx	TRICARE Retail Network
UF	Uniform Formulary
UGT	uridine diphosphate glucuronosyl transferase
VA-HIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
VARR	voluntary agreements for TRICARE retail pharmacy rebates

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

February 2007

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee was briefed on two new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration: sitagliptin phosphate tablets (Januvia) and paliperidone extended release [ER] tablets (Invega). UF consideration was deferred until drug class reviews are completed. No action is required since the P&T Committee did not recommend a quantity limits (QL) or prior authorization (PA) for either of these drugs.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

The John Warner National Defense Authorization Act for FY 2007 directed that the Secretary of Defense conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to prescription alternatives. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program office, selected the proton pump inhibitor (PPI) omeprazole magnesium as the initial OTC product. It is projected to be available at military treatment facilities (MTFs) and the mail order points of service by 1 May 2007.

The P&T Committee previously reviewed the PPIs in February 2005. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-isomer of omeprazole, is non-formulary under the UF. The Basic Core Formulary (BCF) selections in this class are prescription omeprazole and rabeprazole.

Relative Clinical Effectiveness – The P&T Committee concluded (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while FDA-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

Relative Cost Effectiveness – The cost analysis showed that omeprazole magnesium has a cost effectiveness profile similar to prescription omeprazole in the mail order and MTF points of service and a more favorable cost effectiveness profile in the retail sector. Omeprazole magnesium is more cost effective than other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium is comparable in cost to prescription omeprazole, and more cost effective than the other PPIs included on the UF.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR). All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; ramelteon acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

As of December 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month. The SED-1 drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million)—up from #18 in FY 2005 ($72 million), and #20 in FY 2004 ($54 million). Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed SED-1 agent, zolpidem ER, followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appears to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in sleep

duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

2) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

3) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone (Desyrel, generics), based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

4) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

5) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

6) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

7) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, 6 hours (up to 9 hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, 1 hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

8) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

9) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

10) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

11) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

12) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a Drug Enforcement Agency (DEA) scheduled substance.

13) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.

2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.

3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) eszopiclone and zolpidem IR be maintained as formulary on the UF with a PA requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF, with a PA requiring a trial of zolpidem IR for new patients (see paragraphs 6A, 6B, and 6C on pages 23-31 and Appendix D on page 79 of the P&T Committee minutes).

The Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

In order for a patient to receive a non-formulary SED-1 agent at the formulary cost-share, both the PA and medical necessity (MN) criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies or protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for ramelteon, zaleplon, and zolpidem ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) MN criteria for ramelteon, zaleplon, and zolpidem ER (see paragraph 6D on page 31 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an effective date of the greater of 1) the first Wednesday following a 90 day implementation period, or 2) the time necessary to complete logistical arrangements to implement the automated PA. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 6E on pages 31-32 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class (see paragraph 6F on page 32 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into four categories, based on their potency. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of break-through pain, or narcotic analgesics in general for the treatment of neuropathic pain.
2) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], tricyclic antidepressants [TCAs]) in chronic non-cancer pain.
3) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.
4) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels

(~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

5) There is insufficient evidence to support efficacy differences between high potency IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges [Actiq, generic] and buccal tablets [Fentora]). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

6) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

7) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

8) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

9) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days in patients with renal impairment, sickle-cell disease, central nervous system [CNS] disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

10) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns over safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

11) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data

supporting differences in potential for abuse among like medications (e.g., high potency long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

12) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., monoamine oxidase inhibitors [MAOIs] and selective serotonin reuptake inhibitors [SSRIs]); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

13) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

14) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

15) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for "pre-packed" products in commonly dispensed quantities would facilitate inventory and dispensing at their facilities.

16) Clinical coverage considerations support a broad array of formulary agents and formulations.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) that:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch (Duragesic, generics), oxycodone ER (Oxycontin), and oxymorphone (Opana ER) were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they possess unique clinical advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents (morphine sulfate IR and oxycodone

IR), the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER (Ultram ER) was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established QLs for fentanyl transmucosal lozenges, recommendations in Fentora package labeling recommending a maximum of four tablets per day, and current DoD prescribing patterns for Fentora buccal tablets (see paragraphs 7A, 7B, and 7C on pages 35-51 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tramadol ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for tramadol ER (see paragraph 7D on page 51 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 51-52 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating the following medications as the BCF selections in this class: morphine sulfate ER (MS Contin, generics) 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/ APAP 5/325 mg; hydrocodone/APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/ APAP elixir 12/120 mg/5 mL; and tramadol IR 50 mg (see paragraph 7F on page 52 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents available in the U.S. Based on chemical structure and mechanism of action, the drug class was divided into seven subgroups: ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors and combinations with beta blockers; alpha 2 adrenergic drugs; adrenergics; cholinergics; and cholinesterase inhibitors. The ophthalmic glaucoma agent drug class accounted for $51.1 million in MHS expenditures for the period October 2005 to September 2006, and is ranked #34 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) *Prostaglandin analogs* – Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) all decrease intraocular pressure (IOP) from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-benzalkonium (BAK) preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate (Betimol), levobunolol (Betagan, generics), metipranolol (Optipranolol, generics) and carteolol (Ocupress, generics) appear similar based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution (Timoptic XE, generics) reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles.

Betaxolol (Betoptic, generics; Betoptic-S) decreases IOP to a lesser extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamide (Azopt) and dorzolamide (Trusopt) appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however the burning and stinging upon instillation lasts less than ten seconds, diminish over time, and has not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine (Iopidine) is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). In an unpublished trial, brimonidine purite 0.1% (Alphagan P) demonstrated an improved safety and tolerability profile compared to brimonidine BAK 0.2% (generic).

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine (Pilocar, generics; Pilopine HS gel) is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin (Propine), the cholinergics acetyl-choline (Miochol-E) and carbachol (Isopto Carbachol) and the cholinesterase inhibitor echothiophate (Phospholine Iodide) serve unique niches in therapy.

6) Based on clinical issues alone, there are no compelling reasons to classify any of the glaucoma drugs as non-formulary on the UF.

Relative Cost Effectiveness Conclusion: Based on the results of several CMAs, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) The CMAs compared the weighted average cost per day of treatment for each drug product. For the prostaglandin analogs: a) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; b) latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and c) an all-on scenario (i.e., all three prostaglandin products were included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

2) For the other ophthalmic glaucoma agents, only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate (Betimol) and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost

effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol, carteolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution, brimonidine, apraclonidine, dorzolamide, dorzolamide/timolol, dipivefrin, acetylcholine, carbachol, pilocarpine, echothiophate be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide be classified as non-formulary under the UF (see paragraphs 8A, 8B and 8C on pages 52-64 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide (see paragraph 8D on pages 64-65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8E on page 65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5% (Timoptic XE, generics); and pilocarpine (see paragraph 8F on page 65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's Disease and not depression. The three oral MAOI antidepressants were first introduced to the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars in expenditures in FY 2006, which comprises less than 1% of total MHS expenditures for all antidepressant drug classes.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.
2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from dietary tyramine.
3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.
4) Response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline. However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.
5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.
6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hour). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOI antidepressants (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the UF.

Relative Cost Effectiveness Conclusion - The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOI antidepressants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that isocarboxazid, phenelzine and tranylcypromine be maintained as formulary on the UF, and that transdermal selegiline be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 66-71 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for MN criteria for transdermal selegiline, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for transdermal selegiline (see paragraph 9D on page 71 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation

period will begin immediately following approval by the Director, TMA (see paragraph 9E on pages 71-72 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – The P&T Committee had previously determined at the November 2006 meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine be classified as the ECF agent (see paragraph 9F on pages 71-72 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations
Appendix D – FIGURE 1. PA Process for SED-1 Agents Other than Zolpidem IR

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____//signed//_____

MG Elder Granger, USA, MC
Deputy Director, TMA
Date: 02 May 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
February 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 13-14 February 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Lt Col Charlene Reith *for* Lt Col Everett McAllister, BSC	Air Force, Pharmacy Officer
No representative *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC for COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Maj Chang Chinran, NC, USAF	Health Plans Operations, TMA
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR

D. Non-Voting Members Absent

None	

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Mark Geraci, Pharm.D.	VAPBM
Capt Jeremy King, MC, USAF	WHMC

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – November 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of November Minutes - Dr. William Winkenwerder, Jr., M.D., approved the minutes of the November 2006 DoD P&T Committee meeting on 17 January 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the P&T Committee regarding the December 2006 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Status of Exenatide (Byetta) Prior Authorization (PA) – The PEC briefed the members of the P&T Committee on preliminary results of implementing the PA for exenatide, which went into effect 31 January 2007. The exenatide PA represents the first use of the new automated profile review capability in the Pharmacy Data Transaction Service (PDTS), which enables PA criteria to be automated based on a "look-back" at patient profiles during a given period. The percent of patients automatically approved through the automated process during the first few days the exenatide PA was in place was consistent with previous estimates; the process appears to be functioning as designed.

D. Administrative Action: PA Criteria for Exenatide – The PEC notified the P&T Committee of a December 2006 change in Food and Drug Administration (FDA)-approved labeling for exenatide. The new labeling states that exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, *a thiazolidinedione,* a combination of metformin and a sulfonylurea, *or a combination of metformin and a thiazolidine-dione*, but have not achieved adequate glycemic control. Italicized text indicates changes in labeling. The P&T Committee ratified the corresponding changes to exenatide PA criteria made under the auspices of the Executive Council, which were accomplished prior to implementation of the PA on 31 January 2007.

E. Status of Fentanyl Patch PA – The P&T Committee discussed implementation of the PA for fentanyl patch recommended at the November 2006 meeting and approved by the Director, TMA in January 2007. The Committee clarified the "look-back" period and definition of prior opioid use that will be used by the automated PA review process. The specific automated PA criteria that will be applied to all fentanyl prescriptions will be the following:

- Patient is likely to be opioid-tolerant based on receiving at least one prescription for one of the following strong opioids (fentanyl patch, morphine, oxycodone (not including combination products), hydromorphone, methadone, or oxymorphone) during the last 60 days.

The P&T Committee reached this conclusion after reviewing estimates of the number and percent of fentanyl patch patients that would be affected by the PA, including the number of patients who had received fentanyl patch prescriptions during the last 120 days, but not within the last 60 days. The P&T Committee agreed that the best trade-

off between ensuring safety and potentially interrupting therapy for established patients would be to allow pharmacists at retail network pharmacies the ability to override the system warning after determining that the patient could be presumed to be opioid tolerant based on information from the patient or the physician. The retail network pharmacist would also have the option of having Express Scripts, Inc. (ESI) handle the PA by advising patients to have their physicians contact ESI.

F. UF Request Process – The P&T Committee approved a request form to be used by military treatment facility (MTF) healthcare providers requesting consideration of potential changes to the Basic Core Formulary (BCF)**,** Extended Core Formulary (ECF), or UF, including changes to medical necessity (MN) criteria for non-formulary medications, prior authorization criteria, or quantity limits. The three general process points previously agreed upon by the P&T Committee will apply:

- Requests will require review and concurrence by the local MTF P&T Committee.
- Requests will be required to contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.
- Requestors will be required to explain potential conflicts of interest and certify that the request was not initiated or unduly influenced by pharmaceutical industry representatives.

G. Regulatory Status of Pseudoephedrine (PSE) Products – The PEC briefed the committee on the Methamphetamine Anti-Proliferation Act (MAPA), part of the Children's Health Act of 2000; the Combat Methamphetamine Epidemic Act (CMEA) of 2005; and Oregon House Bill 2485 (2005). These three pieces of legislation were enacted to address the diversion of drug products containing PSE, ephedrine and phenylpropanolamine (PPA) for the illicit production of methamphetamine. (PPA has been removed from the human drug market but remains available for veterinary use.)

The CMEA requires pharmacies and other sellers to place PSE products behind the counter; check the identity of purchasers; maintain a log of each sale that includes the purchaser's name and address, signature of the purchaser, product sold, quantity sold, date, and time; maintain the logbook for at least two years; train employees in the requirements of the law; and certify to the Drug Enforcement Agency (DEA) that the training has occurred. Most states have enacted similar legislation.

The State of Oregon passed Oregon House Bill 2485 (2005), which stipulated that the State Board of Pharmacy designate PSE as a Schedule C-III controlled substance. This designation imposed a limit of 90 days supply for a prescription in the State of Oregon. It also requires that refills be filled within 180 days of prescription origin. The bill does not prohibit over-the-counter (OTC) sales, which continue to be subject to requirements of the CMEA. This bill affected 74 individuals in the TRICARE mail order pharmacy and 800 users in the retail point of service. Oregon patients receiving PSE products by prescription are now required to obtain a new prescription every six months.

As part of the review for this presentation, the PEC contacted eight Army and Navy MTFs to determine the regulatory impact on DoD OTC programs. Air Force policy prohibits OTC programs. Directors of four programs previously removed PSE off the drug list for OTC dispensing. Of facilities supplying PSE, all have QLs, require photo identification, and most require a signature. Navy policy requires entry of any of the drugs obtained from an OTC program into the patient's CHCS profile. Army policy does not require CHCS entries. Entry into the patient's CHCS profile would exceed the CMEA logbook requirement. Neither service has a program in place to meet the training requirements specified in the CMEA.

The P&T Committee agreed that there is little chance that large amounts of PSE could be diverted from MTF pharmacies. Mandatory logbook and training requirements are best addressed by the Pharmacy Service consultants/specialty leaders.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on two new drugs, sitagliptin (Januvia) and paliperidone extended release [ER] tablets (Invega), which were approved by the FDA (see Appendix B). The P&T Committee determined that these two new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product.

OTC drugs provided under the demonstration project shall be made available through MTFs and the TRICARE mail order pharmacy. The demonstration will begin no later than 1 May 2007, and will last for a time period at least as long as the current contract, but no longer than five years.

Omeprazole magnesium is the first medication proposed for inclusion in the OTC Demonstration Project. Since this is the first opportunity for omeprazole magnesium to be considered for inclusion on the UF, it was reviewed as a new drug in a class already reviewed.

The P&T Committee previously reviewed the proton pump inhibitors (PPIs) in February 2005. These medications suppress secretion of gastric acid by irreversibly inhibiting H+, K+ ATPase (the proton pump) in gastric parietal cells. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-

isomer of omeprazole, is non-formulary under the UF. The BCF selections in this class are prescription omeprazole and rabeprazole.

1) *Relative Clinical Effectiveness* – Prescription omeprazole, first approved in 1987, is indicated for short-term treatment of active duodenal ulcer, benign gastric ulcer, and endoscopically-diagnosed erosive esophagitis; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease; maintenance of healing of erosive esophagitis; long-term treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome; and for eradication of *H. pylori* infection (in combination with clarithromycin). Recommended doses range from 20 mg to 60 mg per day. It is available in 10-, 20-, and 40-mg delayed release capsules.

   Omeprazole magnesium was approved as an OTC medication in June 2002 based on placebo-controlled trials that found it to be effective in the treatment of recurring heartburn. It is labeled as a 14-day once-daily course of treatment for frequent heartburn (occurring two or more times per week), which may be repeated every four months. Each 20.6 mg delayed release tablet of omeprazole magnesium is equivalent to 20 mg of omeprazole. There is no reason to believe that the pharmacology or pharmacokinetics of omeprazole magnesium differ from prescription omeprazole.

   Common adverse events reported with the use of omeprazole magnesium include headache, diarrhea, and elevations in liver enzymes. Rare but severe adverse events include liver injury, bone marrow suppression, Stevens-Johnson syndrome, and hypersensitivity. Omeprazole magnesium is Pregnancy Category C. It is not recommended for patients under 18 years of age.

   Conclusion: The P&T Committee concluded that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while Food and Drug Administration (FDA)-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the PPI class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that omeprazole magnesium has similar efficacy, safety, tolerability, and clinical outcomes compared to the existing drugs in the PPI class.

   The cost review for omeprazole magnesium compared the cost per unit across all three points of service to the other PPIs.

Conclusion: The results of the cost review showed that omeprazole magnesium is cost effective on a per unit basis when compared to generic prescription omeprazole in the mail order and MTF points of service. Omeprazole magnesium is more cost effective when compared to generic prescription omeprazole in the retail point of service. Omeprazole magnesium is more cost effective when compared to other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service.

3) *Clinical and Cost effectiveness Conclusions* – The P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary under the UF.

4) *MN Criteria* – Since omeprazole magnesium was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since omeprazole magnesium was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR).

All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; they bind to benzodiazepine gamma-aminobutyric acid (GABA) receptors in the brain, but at a different site than the benzodiazepines. Ramelteon is mechanistically different; it acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

The newer sedative hypnotics are preferred to benzodiazepines (the second most commonly used drug for insomnia) primarily due to a more favorable adverse effect profile and lower potential for abuse. They are widely used worldwide. Other medications for insomnia include sedating antidepressants such as trazodone, sedating antihistamines such as diphenhydramine, and other rarely used medications (e.g., chloral hydrate).

Utilization of the SED-1 agents is increasing rapidly in DoD. As of Dec 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month; the drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million) – up from #18 in 2005 ($72 million), and #20 in 2004 ($54 million). Retail network

pharmacies dispense about three times more tablets than do MTFs and approximately five times more than mail order. Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed agent, zolpidem ER. Zolpidem ER is followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

A. SED-1s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the SED-1 agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Insomnia is the most common sleep complaint across all stages of adulthood. Prevalence increases with age, from an estimated 10% of the younger adult population to up to 50% of elderly adults. Treatment includes both pharmacologic and non-pharmacologic approaches; however, non-pharmacologic treatments such as cognitive behavioral therapy are often not available to patients due to the need for extensive clinical contact. Patients should receive instruction on sleep hygiene measures (such as removing distractions from the sleeping area and avoiding stimulants at bedtime).

1) Efficacy

Many clinical trials compare the newer sedative hypnotic agents to placebo; some of these trials include an active comparator (most commonly zolpidem IR in addition to placebo. There are also many published trials comparing these agents to benzodiazepines. Two studies compare zolpidem IR to trazodone (Desyrel, generics), an antidepressant commonly used for insomnia.

In addition to measures of sleep onset and duration, the Committee also reviewed data assessing effect on quality of life, since the ultimate goal of treating insomnia is to improve overall health and well-being, not merely to increase the number of minutes spent asleep.

Based on this information, the P&T Committee came to the following conclusions:

- All SED-1 agents improve sleep latency (the amount of time it takes to fall asleep) compared to placebo, based on both polysomnographic measures (monitoring performed in a sleep lab) and subjective measures (as reported by patients). The amount of improvement compared to placebo appears similar among all of the agents. Data supporting the effect of ramelteon on sleep

latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Published data with zolpidem ER are also limited, with a single published trial, but sleep latency data appear similar to the IR formulation and pharmacokinetic studies show little or no difference in initial drug concentrations.

- Zolpidem IR and eszopiclone appear to consistently improve total sleep time and awake time after sleep onset (or the amount of time spent awake after initially falling asleep) to a similar degree versus placebo. Zaleplon and ramelteon do not consistently demonstrate increases in measures of sleep duration.
- Zolpidem ER is a controlled release version of zolpidem consisting of a two-layer tablet providing an IR phase followed by a prolonged release phase. The formulation is intended to retain the onset and elimination characteristics of zolpidem IR while maintaining plasma concentrations three to six hours post-dose. Time versus concentration curves comparing zolpidem ER to zolpidem IR show comparable initial concentrations followed by higher concentrations of zolpidem ER during this time period. However, it is unclear whether this is associated with a clinically significant increase in sleep duration, as clinical trial data comparing zolpidem IR and ER are not available and reported effects on sleep duration with zolpidem ER do not appear markedly different from results from zolpidem IR trials.
- Trials including two or more SED-1 agents (usually compared to placebo) include three published trials comparing zaleplon and zolpidem IR to placebo and one unpublished trial obtained from the FDA statistical review of eszopiclone that included eszopiclone and zolpidem IR. Based on these trials, zaleplon decreased sleep latency to a greater degree than zolpidem IR (8-24 minutes for zaleplon versus 6-13 minutes for zolpidem IR, but zolpidem IR increased total sleep time more than zaleplon (28-42 minutes for zolpidem IR versus 7-27 minutes for zaleplon). More rebound insomnia was noted with zolpidem IR on the first night after discontinuation. The FDA statistical review for eszopiclone reported very similar results for eszopiclone versus zolpidem IR with respect to sleep latency, total sleep time, and awake time after sleep onset.
- Based on trials comparing zolpidem IR and zopiclone (eszopiclone's racemic parent drug) to benzodiazepines, the newer sedative hypnotics appear to be similar in efficacy to the benzodiazepines. Short-term adverse events appear similar based on published trials; however, there appears to be more rebound insomnia with benzodiazepines than with the newer sedative hypnotics.
- A single comparative trial of zolpidem IR versus trazodone in adult insomnia sufferers without co-morbid depression demonstrated similar efficacy during the two weeks of the study; although trazodone may result in greater daytime somnolence than zolpidem IR.

- In regard to improvement of sleep architecture, there are no consistent data to demonstrate that the newer sedative hypnotics increase the length of time spent in the stages of sleep associated with restorative sleep to a degree that is clinically significant, compared to placebo.
- The most extensive data supporting long-term efficacy and safety are for eszopiclone, which has data from a 6-month randomized controlled trial (RCT) and open label data out to one year. Zolpidem IR has data from RCTs indicating continued efficacy and safety over 35 nights of nightly use and 84 nights of non-nightly use, with open label data out to one year. No long-term data are available for zolpidem ER, which was only tested in short-term trials (three weeks), although it is probably reasonable to expect long-term results similar to zolpidem IR (Ambien). Zaleplon RCT data are limited to 4-week trials, although open label data supporting efficacy and safety for up to one year are available in elderly patients. Ramelteon has shown sustained efficacy and safety for up to five weeks in RCTs, with open label data out to one year.
- Improvement in overall quality of life as a function of improved sleep was not usually addressed in either short- or long-term clinical trials. However, a few trials employed quality of life assessment tools, with one of the most useful measures being the standardized short-form 36 (SF-36) questionnaire. Two non-nightly zolpidem IR studies demonstrated a minimal improvement on certain aspects of the SF-36 after treatment, but no difference from placebo on other aspects. Two eszopiclone studies that included pre and post-treatment questionnaires addressing improvement in overall sense of well-being showed no significant improvement versus placebo. The Committee concluded that there is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although there limited are data showing improvement in certain aspects of quality of life. There are insufficient comparative data to draw conclusions about individual agents.

2) Safety / Tolerability

- The SED-1 agents, including both the benzodiazepine receptor agonists and ramelteon, appear to have similar adverse effect profiles, most commonly drowsiness, dizziness, and headache. Rates of discontinuation due to adverse events during clinical trials were similar among the SED-1 agents, ranging from about 2-6% in short-term trials. Adverse effects and discontinuation rates due to adverse events were similar in comparative trials (zolpidem IR versus zaleplon; eszopiclone versus zolpidem IR). An unpleasant taste was consistently reported with eszopiclone during clinical trials, occurring in about 26.1% of patients receiving eszopiclone versus 5.6% with placebo over the course of a 6-month trial.
- Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer elimination half-lives tend to pose a greater risk for these effects. Particularly

notable is the 6-hour half-life of eszopiclone, which may extend to nine hours in elderly patients, compared to half-lives of about one hour for zaleplon, 1-2.6 hours for ramelteon and 2.5-2.8 hours for zolpidem (Ambien, Ambien CR). Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

- Driving safety studies report impaired performance and increased risk of accidents with eszopiclone's racemic parent drug zopiclone (widely used outside the U.S.) at a 7.5 mg daily dose. The applicability of these data to eszopiclone is unclear, since the usual younger and elderly adult dosing strengths of eszopiclone (3 and 2 mg, respectively) would be equivalent to zopiclone doses lower than 7.5 mg. Product labeling and marketing for eszopiclone advises against taking the product unless the patient is able to get eight or more hours of sleep; adherence to this warning is advisable. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects (morning sleepiness, daytime alertness, daytime ability to function), based on results of one unpublished trial reported in the FDA statistical review of eszopiclone.
- Because of its very short half-life, a repeat dose of zaleplon may be taken after the patient has had difficulty falling asleep, as long as the patient is able to sleep for four or more hours. Driving studies with zaleplon 10 and 20 mg showed no significant effects on morning driving even after middle-of-the-night administration. Since the risk of falling and hip fracture tend overall to increase with increasing half-life, zaleplon may have an advantage in elderly patients. However, this is not a simple relationship and prescribers must take into account patient activity patterns; short half-life agents may be more likely to cause falls during the early part of the night.
- In other special patient populations, it is difficult to see major advantages or disadvantages for any one agent. All are hepatically metabolized and carry warnings about use and/or recommendations for dose adjustment in patients with hepatic dysfunction; pharmacokinetic parameters do not appear to be substantially affected by renal dysfunction. All are Pregnancy Category C. Little data is available concerning use in pediatric patients; there is some concern about chronic or chronic intermittent use of ramelteon in pediatric patients due to effects on prolactin and testosterone levels that are not felt to be clinically significant in adults.
- The most prominent withdrawal symptom upon discontinuation of the SED-1 agents is probably rebound insomnia, or worsening of insomnia compared to the patient's pre-treatment baseline; other withdrawal symptoms may also occur. Rebound insomnia typically occurs only in the first night after discontinuation. Occurrence of rebound insomnia has been reported in clinical trials with all of the SED-1 agents except ramelteon. Based on three trials, more rebound insomnia on the first night after discontinuation was noted with zolpidem IR versus zaleplon.

- All of the newer sedative hypnotics, with the exception of ramelteon, probably have a small, but significant potential for abuse, although this is likely to be rare in patients without psychiatric disorders or previous history of substance abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients with a high risk of substance abuse. Ramelteon is the only agent in this class that is not a DEA scheduled substance.
- No major comparative disadvantages were noted among the agents based on potential for drug-drug interactions. All are affected by potent CYP 3A4 inducers or inhibitors and have predictable additive effects if given with alcohol or other medications that can impair psychomotor performance. Cimetidine (Tagamet, generics) markedly increases levels of zaleplon due to inhibition of two metabolic pathways (CYP 3A4 and aldehyde oxidase); the initial dose of zaleplon should be decreased. The major metabolic route for ramelteon is CYP 1A2; ramelteon is contraindicated with the potent 1A2 inhibitor fluvoxamine (Luvox, generics) and may be less effective in smokers, since smoking is a 1A2 inducer.

3) Other Uses

Based on its effects on the sleep-wake cycle, ramelteon may have a niche in therapy for time zone shifting in travelers, or for phase shifting in shift workers, but data at this point are limited.

4) Provider Opinion

A total of 173 DoD healthcare providers responded to a survey regarding the SED-1 agents; 72% of responders were physicians, 22% pharmacists, 5% physician assistants or advanced practice nurses, and 1% other. The most common specialties were psychiatry (25%), pharmacists (22%), and family practice, internal medicine, or general practice (21%). The vast majority of responders (97%) indicated that they had zolpidem IR on their local formulary, but relatively few indicated that other SED-1 agents were on formulary (zolpidem ER 18%, ramelteon 3%, eszopiclone and zaleplon 0%).

The majority of responders estimated that between 40 and 79% of patients could be successfully treated with their first choice of agents. Most (71%) would treat patients failing the first agent with another SED-1 agent; the majority estimated that between 20 and 59% of patients could be successfully treated with the second agent. The majority of responders estimated that fewer than 20% of patients discontinue therapy due to adverse events.

5) Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in

sleep duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

b) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

c) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone, based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

d) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

e) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

f) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

g) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, six hours (up to nine hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, one hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

h) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

i) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

j) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

k) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

l) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a DEA scheduled substance.

m) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. SED-1s – Relative Cost Effectiveness

In considering the relative cost effectiveness of agents within this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Given the overall clinical conclusion that the agents within the SED-1 class have similar relative clinical effectiveness, a cost-minimization analysis (CMA) was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

The CMA for the SED-1 class revealed the following cost effectiveness rank-order (from most to least cost effective): 1) eszopiclone; 2) ramelteon; 3) zaleplon; 4) zolpidem IR; and 5) zolpidem ER. Although zolpidem IR was not as cost effective as eszopiclone in this CMA, the P&T Committee noted that zolpidem IR is scheduled to become generically available on 21 April 2007 and will likely become the most cost effective agent within the class shortly thereafter.

A budget impact analysis (BIA) of various UF formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, and non-formulary cost-shares). The goal of the BIA was to aid the P&T Committee in determining which group of SED-1 agents best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

The BIA also considered the cost effectiveness of implementing a prior authorization (PA) that requires a trial of zolpidem IR for patients starting treatment with a SED-1 agent. This PA would incorporate the automated PA capability in PDTS in order to "look-back" at the patient's profile during the last 180 days. Based on this automated review, TRICARE would cover prescriptions for a SED-1 agent other than zolpidem IR if the patient had received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days. Patients who had not received a SED-1 agent prescription during the last 180 days would be required to meet PA criteria for any SED-1 agent other than zolpidem IR (Ambien). (See Appendix D.)

Cost Effectiveness Conclusion

The P&T Committee concluded that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.
2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.
3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusion stated above.

C. SED-1s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) zolpidem IR and eszopiclone be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF with a PA requiring a trial of zolpidem IR for new patients.

The P&T Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

The P&T Committee noted that in order for a patient to receive a non formulary SED-1 agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies and protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

D. SED-1s – MN Criteria

Based on the clinical evaluation for ramelteon, zaleplon, and zolpidem ER, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for ramelteon, zaleplon, and zolpidem ER:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

The P&T Committee noted that while zolpidem IR and eszopiclone would both be considered formulary alternatives, a trial of zolpidem IR would be required for patients who had not received a SED-1 prescription in the last 180 days at an MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order).

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the MN criteria outlined above.

E. SED-1s – UF Implementation Period

Approximately 40,447 patients (21% of all SED-1 patients) would be affected by the recommended non-formulary selections in this drug class. This figure includes both patients who have previously received SED-1 agents, as well as new users starting on SED-1 agents. Based on the number of new users and the current percentage of new users receiving SED-1 agents other than zolpidem IR in retail (50%) and mail (40%), the prior authorization for SED-1 agents other than zolpidem IR would affect approximately 12,500 users per quarter, or 50,000 annually.

The P&T Committee noted that this would be the first time a PA including the newly available automated review process had been established in a class also including non-formulary agents and that many operational details of the process had yet to be worked out. Accordingly, the P&T Committee voted to recommend an implementation period of the greater of 1) the first Wednesday following a 90-day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

MTFs will not be allowed to have ramelteon, zaleplon, or zolpidem ER on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary SED-1 agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an implementation period of the greater of 1) the first Wednesday following 90 day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

F. SED-1s – BCF Review and Recommendations

The P&T Committee considered the BCF status of the SED-1 Agents. Currently there are no SED-1 agents on the BCF; the P&T Committee had previously determined at the August 2006 meeting that at least one SED-1 agent would be placed on the BCF. Zolpidem IR is widely used at MTFs, has clinical data supporting efficacy both for decreasing sleep latency and increasing sleep duration, is clinically similar to other SED-1 agents with respect to safety and tolerability, and is expected to become the most cost effective SED-1 agent after it becomes generically available (anticipated date: 21 April 2007). The P&T Committee agreed that zolpidem IR should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class.

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into the following categories, based on their potency (as reflected by their DEA status) and whether or not they are combined with a non-opioid analgesic, as outlined in Table 1. These categories do not take into account all differences among agents, but serve to reduce the large number of available agents into manageable categories. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

By category, the majority of MHS narcotic analgesic prescriptions during FY 2006 (59%) were for the lower potency opioid combinations, which are widely prescribed following

Table 1: Narcotic Analgesic Categories & BCF Listings as of Feb 2007

Category	Medications	BCF Agents (Feb 07)
High potency Opioids (Schedule II Agents) – Single Analgesic Ingredient	▪ Codeine* - tablets, solution, injection ▪ **Fentanyl** – transdermal (Duragesic), transmucosal lozenges (Actiq), buccal tablets (Fentora) ▪ Hydromorphone – injection, tablets, liquid ▪ Levorphanol – tablets, injection ▪ Meperidine – tablets, solution, injection ▪ Meperidine / promethazine – capsules ▪ Methadone – oral concentrate, solution, tablet, injection ▪ **Morphine –** IR tablets, 12-hr ER tablets (MS Contin, generics; Oramorph SR), 24-hr ER capsules (Avinza, Kadian), solution, suppositories, injection ▪ Opium - tincture; opium / belladonna alkaloids – suppositories ▪ **Oxycodone –** IR capsules, oral concentrate, solution, 12-hr ER tablets (Oxycontin), IR tablets ▪ Oxymorphone – IR tablets (Opana); 12-hr ER tablets (Opana ER)	Morphine sulfate 15 mg, 30 mg and 60 mg 12-hour extended release tablets (MS Contin, generics; excludes 100 and 200 mg strengths)
High potency (Strong) Opioids (Schedule II Agents) – Analgesic Combos	▪ **Oxycodone/** APAP – tablets, capsules, solution ▪ Oxycodone / ASA – tablets	Oxycodone 5 mg/APAP 325 mg and/or 500 mg oral
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Single Analgesic Ingredient Agents	▪ Buprenorphine – injection (sublingual tablets not included in class) ▪ Butorphanol – nasal spray, injection ▪ Pentazocine / naloxone – tablets ▪ Propoxyphene – capsules, tablets ▪ Nalbuphine (not controlled) – injection ▪ **Tramadol** (not controlled) **–** IR tablet, 24-hr ER tablets (Ultram ER)	None
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Analgesic Combos	▪ **Codeine / APAP –** tablets, elixir, oral suspension ▪ Codeine / ASA – tablets ▪ Codeine / ASA / carisoprodol - tablets ▪ Codeine / caffeine / butalbital / APAP – capsules ▪ Codeine / caffeine / butalbital / ASA – capsules ▪ Dihydrocodeine / caffeine / APAP – capsules, tablets ▪ Dihydrocodeine / caffeine / ASA – capsules ▪ **Hydrocodone / APAP** – capsules, solution, tablets ▪ Pentazocine / APAP – tablets ▪ **Propoxyphene / APAP** – tablets ▪ Propoxyphene / ASA / caffeine – capsule ▪ **Tramadol / APAP** (not controlled) – tablets	Codeine/APAP oral

* Pharmacologically and therapeutically, codeine is usually referred to as a weak opioid; however, single ingredient codeine formulations are classified by the DEA as Schedule II medications (C-IIs) and are so classified in this table. The most commonly used medications are bolded.
APAP = acetaminophen; ASA = aspirin; ER = extended release; IR = immediate release

injuries or medical / dental procedures; followed by high potency opioid combos (19%); high potency single analgesic products (13%); and lower potency opioid single analgesic products (9%). The majority of expenditures during this time period, however, were for the high potency single analgesic products (67%), followed by the lower-potency opioid combinations (20%), the high potency opioid combinations (8%), and the lower-potency single analgesic products (5%). This reflects the relatively higher cost and more intensive treatment regimens associated with the high potency single analgesic products used for chronic treatment of pain, some of which are still brand-only medications.

Pharmacologically, the narcotic analgesics act at opioid receptors (mu, kappa, and delta), inhibiting excitatory neurotransmission of substance P, acetylcholine, norepinephrine, dopamine, and GABA by blocking voltage-dependent calcium channels. Analgesia is mediated through changes in the perception of pain at the spinal cord (mu_2, delta, kappa receptors) and higher levels in the central nervous system (CNS) (mu_1 and kappa

receptors). Narcotic analgesics also have effects on the endocrine and immune systems. Stimulation at the mu receptor produces euphoria, respiratory depression, and physical dependence. In addition to acting at mu receptors, tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake, resulting in inhibition of pain transmission in the spinal cord (similar to monoamine oxidase inhibitors [MAOIs] or tricyclic antidepressants [TCAs]).

Narcotic analgesics are primarily indicated for the treatment of mild, moderate and severe pain. Use correlates with potency, with the higher potency agents (e.g., morphine, oxycodone, fentanyl) used in more severe pain and lower potency agents and combinations with non-opioids used for less severe pain. Some narcotic analgesics have specific clinical niches:

- Opium is used in combination with the anticholinergic belladonna for the treatment of pain caused by ureteral spasm; more effective and/or safer agents have largely replaced the use of opium tincture for diarrhea.
- Use of meperidine, a short-acting narcotic analgesic primarily given parenterally due to poor oral absorption, is limited to acute pain situations due to a neurotoxic metabolite that can cause anxiety, tremors, myoclonus, and generalized seizures with repetitive dosing.
- Methadone is used for detoxification and maintenance treatment of narcotic addiction, but also for chronic pain.
- The nasal formulation of butorphanol is used primarily for migraine headache; this product was initially released as a non-scheduled product, but was subsequently scheduled as a C-IV controlled substance following multiple reports of abuse.
- Tramadol has a lower potential for abuse or respiratory depression than other narcotic analgesics, lacks significant cardiac effects, and is not associated with peptic ulcer disease, making it an alternative in patients who cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs). Due to its dual mechanism of action, tramadol may have a more prominent place in the treatment of neuropathic pain than other narcotic analgesics.

The majority of the narcotic analgesics are IR and/or short-acting medications most commonly used on an every four to six hour basis. Longer duration products include fentanyl transdermal patches (Duragesic, generics), which are applied every 72 hours; morphine, which is available in 12-hour (MS Contin, generics; Oramorph SR) and 24-hour ER formulations (Avinza, Kadian); oxycodone, which is available in a 12-hour ER formulation (Oxycontin); oxymorphone, which was recently approved as a 12-hour ER formulation (Opana ER), tramadol, which is available in a once daily ER formulation (Ultram ER), and methadone, which may be dosed less frequently when given chronically, due to a depot effect. Levorphanol has a long half-life and an extended duration of action (four to eight hours), but its use is limited by sedation and concerns about drug accumulation.

Pure opiate agonists may be categorized by their chemical structure as phenanthrenes (codeine, hydromorphone, morphine, and oxycodone; phenylpiperidines (fentanyl, meperidine); or diphenylheptanes (methadone, propoxyphene). They are therapeutically

classified as either strong opiates (hydromorphone, morphine, methadone, and oxycodone) or weak opiates (codeine, hydrocodone, and propoxyphene). Use of mixed agonist antagonists (e.g., buprenorphine, nalbuphine, butorphanol, and pentazocine) is limited by ceiling analgesia effects and the risk of inducing withdrawal symptoms and recurrence of pain in patients taking chronic opioids.

Tolerance to the adverse effects of narcotic analgesics, including respiratory depression, occurs with chronic use. Tolerance to therapeutic effects requiring dose escalation also occurs; some patients may require very large doses of narcotic analgesics to control their pain. Patients often require changes in chronic opioid therapy to address adverse effects or lack of efficacy; switching or rotating different opioids (opioid rotation) has been proposed as a strategy to obtain optimal pain control with minimum adverse effects.

Combination products including both a narcotic analgesic and non-opioid analgesic (most commonly acetaminophen) provide additive analgesic effects, but also limit the possible dose of the narcotic analgesic due to potential toxicity and dosing limits associated with the non-opioid component (e.g., no more than 4 grams of acetaminophen daily). They are not well suited for the treatment of chronic pain.

Standard tables of equianalgesic doses are available to assist clinicians in safely switching between long-acting opioids, typically by converting the total 24-hour dose to an equivalent amount of morphine and from there to the appropriate 24-hour dose of the new opioid. This process is complicated by wide intra-patient variability in response and incomplete cross-tolerance among opioids; for this reason, recommended conversions are usually conservative and titration of the new opioid is likely to be required. Disparate methodologies in calculating equianalgesic doses for transdermal fentanyl, levorphanol and methadone exist; these agents may be more difficult to titrate than other narcotic analgesics.

A. Narcotic Analgesics – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the narcotic analgesics class. Narcotic analgesics were divided into the categories outlined in Table 1, based on DEA schedule, potency, and whether or not the analgesic is a combination agent. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The clinical efficacy review was divided into two major areas: chronic pain (cancer, non-cancer, or neuropathic) and acute pain (post-operative or non-specific). Because ample information is available for most of these agents, the review focused primarily on published meta-analyses, systematic reviews, and well-accepted tertiary literature sources, including clinical practice guidelines. A more detailed review of the literature was performed for specific issues affecting potential formulary decisions.

No single systematic review, meta-analysis, or clinical practice guideline addresses the use of narcotic analgesics to treat all types of chronic and acute pain. Sources included:

- *Chronic cancer pain* – Available cancer pain studies are in general too heterogeneous to conduct systematic reviews. The review included applicable conclusions from a 2001 Agency for Healthcare Research and Quality (AHRQ) technical report, a meta-analysis of four evaluable trials comparing long-acting oxycodone to morphine and hydromorphone [Reid *et al.*, 2006], and head-to-head trials and data analyses comparing two or more narcotic analgesics published since the AHRQ report. Sources of clinical practice guidelines for the treatment of cancer pain include the World Health Organization, the American Pain Society, and the University of Texas MD Anderson Cancer Center.
- *Chronic non-cancer pain* – The most useful reference for the treatment of chronic non-cancer pain was the Drug Effectiveness Review Project (DERP) review of long-acting opioid analgesics for non-cancer pain, last updated July 2006 [Chou *et al.*, 2006]. This review included all drugs reviewed here except for hydrocodone, levorphanol, and the agonist-antagonist agents. In addition, the review included a meta-analysis [Furlan *et al.*, 2006] comparing "weak" opioids (tramadol, propoxyphene, codeine) and "strong" opioids (morphine, oxycodone) to other agents in chronic pain patients primarily suffering from chronic non-cancer pain (osteoarthritis, rheumatoid arthritis, or low back pain), as well as clinical trials assessing the efficacy of the two available fentanyl formulations for breakthrough pain (buccal tablets and transmucosal lozenges). Sources of clinical practice guidelines for the treatment of chronic non-cancer pain included the American Society of Interventional Pain and VA/DoD.
- *Chronic neuropathic pain* – Clinical evidence specifically addressing the use of narcotic analgesics in chronic neuropathic pain is limited; the most useful review was considered to be the one conducted by Finnerup *et al.* (2005) in an attempt to construct an evidence-based algorithm for the treatment of neuropathic pain. The review also included a meta-analysis of trials assessing the efficacy of morphine, methadone, and oxycodone for neuropathic pain and published treatment recommendations from an expert panel group.
- *Acute pain* – There is little literature addressing the use of narcotic analgesics for non-specific acute pain. Consensus statements from the American Pain Society and the American Society for Pain Management Nursing support the appropriate use of "as needed" dosage range orders for narcotic analgesics in the treatment of acute pain. With respect to postoperative pain, the review relied heavily on the Bandolier Oxford League Table of Analgesic Efficacy, which is based on data compiled from single-dose studies in patients with moderate to severe pain. The review also provided clinical trial data or the results of Cochrane reviews for agents not included in the League table and recommendations from the VA/DoD Clinical Practice Guideline for the Management of Postoperative Pain.

1) Efficacy

a) Chronic pain

The clinical review divided chronic pain into three types, based on etiology: cancer pain, non-cancer pain, and neuropathic pain (considered separately from other causes of non-cancer chronic pain).

Treatment algorithms for chronic cancer pain typically start with non-opioids (e.g., NSAIDs, acetaminophen); progress to weak opioids such as codeine or hydrocodone, normally in combination with the non-opioid (some algorithms skip this step depending on pain severity); and then progress to around-the-clock treatment with long-acting high potency single analgesic agents plus IR opioids for breakthrough pain.

There is less consensus about the use of chronic opioids in patients with non-cancer pain (e.g., low back pain, rheumatoid arthritis, osteoarthritis), although various professional organizations have endorsed judicious use of opioids in patients with refractory chronic non-cancer pain. Recommended treatment algorithms are similar to chronic cancer pain.

The categories of drugs most pertinent to treatment of chronic pain are likely the high potency long-acting agents used on an around-the-clock basis for the treatment of constant pain, and the high potency IR agents, which are used for the treatment of breakthrough pain occurring despite treatment with long-acting agents. The most commonly used medications are long-acting and IR formulations of morphine, oxycodone, and fentanyl.

The placement of narcotic analgesics in treatment guidelines for neuropathic pain appears controversial; discussion of the topic is complicated by the fact that some authors consider tramadol to be an opioid and some do not. In general, narcotic analgesics are regarded as third-line agents after TCAs and gabapentin/pregabalin, although at least one set of treatment recommendations lists them among other agents as potential first-line choices.

iii) Clinical evidence in constant cancer pain

Available cancer pain studies are in general too heterogeneous to conduct systematic reviews and many are small and of poor quality. The 2001 AHRQ technical report provided an extensive review of cancer pain literature that served to highlight the limited data available. Out of nine trials, one reported oxycodone to be less effective than morphine, but equally or more often preferred by patients; one reported tramadol to be similar to morphine in efficacy and patient preference (nurses thought pain control was better with morphine but tramadol more tolerable); two reported methadone to be as effective as morphine; one reported buprenorphine as effective as morphine; and one reported propoxyphene to be more effective than low-dose morphine. Eight studies comparing sustained (12-hour formulations) and IR morphine found no difference in efficacy.

Head-to-head comparative trials, one meta-analysis, and a pooled analysis of transdermal fentanyl data published since the AHRQ report add little additional information. A meta-analysis of four randomized double-blind controlled trials found no differences in mean pain scores between oxycodone and either morphine or hydromorphone. An open-label trial comparing transdermal fentanyl to sustained release (every 12-hour) morphine found no differences in efficacy; the percentage of patients reporting constipation and withdrawals due to adverse effects favored transdermal fentanyl. A pooled analysis of transdermal fentanyl data reported similar results, with withdrawals due to adverse effects of 16% with transdermal fentanyl versus 23% with morphine ($p<0.001$). A 4-week trial comparing methadone and morphine reported similar efficacy, but a higher withdrawal rate with methadone (22% versus 6%, $p=0.019$). Two open-label crossover trials involving oxymorphone (Opana ER) versus morphine or oxycodone sustained release reported similar efficacy and concluded that patients could safely be switched from these medications to ER oxymorphone.

The 24-hour ER morphine products (Avinza and Kadian) are purported to have distinct advantages compared to 12-hour ER morphine products, including continuous pain relief, reduced sleep disturbance, ease of use, and fewer reported side effects. These benefits have not been shown to be statistically or clinically significant based on head-to-head trials with 12-hour ER morphine. Trials comparing Kadian or Avinza to 12-hour ER morphine have demonstrated bioequivalence (i.e., 12-hour ER morphine given as 45 mg every 12 hours = 90 mg of Avinza every 24 hours). There are no published trials directly comparing the two 24-hour ER products.

The two products do have some differences. Avinza is a capsule containing both IR and ER beads of morphine sulfate. Therapeutic serum levels are achieved rapidly (~0.5 hour) and then maintained for 24 hours. At steady state, plasma concentrations remain constant (no peak-trough phenomenon). Avinza is restricted to a maximum dose of 1600 mg daily, since it contains fumarate and can cause renal toxicity. Alcohol, including alcohol-containing medications, cannot be taken with Avinza, since this can lead to a rapid dissolution of the ER granules and premature release of morphine.

Kadian capsules contain polymer-coated ER pellets of morphine sulfate, which release morphine slowly within the gastrointestinal tract. The time to achieve maximum serum levels (~9.5 hours) is much longer than with 12-hour ER morphine (2-3 hours) or Avinza (~0.5 hours).

Both products can be opened and sprinkled onto applesauce for patients who have trouble swallowing pills. Kadian granules can also be suspended in water and administered down a large bore (≥16 French) gastrostomy tube, which is not possible with 12-hour ER morphine or oxycodone products.

iv) Clinical evidence in constant non-cancer pain

The DERP report on long-acting narcotic analgesics for non-cancer pain included products requiring dosing three or fewer times per day, including transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine, dihydrocodeine, and oxymorphone.

- Based on direct evidence from head-to-head studies, the report found no differences between agents overall. Evidence included three RCTs comparing transdermal fentanyl and long-acting morphine (two fair-quality trials showed similar efficacy, one poor quality trial showed greater efficacy for transdermal fentanyl); one RCT showing similar efficacy for long-acting morphine once-daily versus twice daily; and one RCT showing equal efficacy between long-acting oxymorphone and long-acting oxycodone.
- Reviewers found no useful indirect evidence concerning comparative efficacy based on 20 clinical trials comparing narcotic analgesics to other agents or placebo; withdrawal rates did not suggest tolerability advantages for any one product.
- Reviewers further found no evidence to suggest greater efficacy for long-acting versus short-acting opioids, based on seven fair-quality trials. Based on three of these trials, they concluded that there was fair evidence that long- and short-acting oxycodone were equally effective for pain control.

A 2006 systematic review [Furlan *et al.*, 2006] included data from 41 trials of opioids (codeine, morphine, oxycodone, tramadol, or propoxyphene) for the treatment of chronic non-cancer pain. Results from a meta-analysis of 28 placebo-controlled trials favored opioids. A meta-analysis of eight trials comparing opioids to other agents (NSAIDs, TCAs) found no significant difference overall, although strong opioids (oxycodone, morphine) were significantly more effective than other agents. The review outlined adverse effect rates with opioids but did not provide useful detail regarding comparison of different agents.

A systematic review of eight trials [Devulder *et al.*, 2005] assessing functional and quality of life outcomes in patients with chronic non-cancer pain in general reported favorable results with opioids, but studies were too heterogeneous to allow comparison of agents.

v) Clinical evidence in breakthrough pain

Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. Narcotic analgesics offering both a long-acting formulation and a short-acting formulation include morphine, oxycodone, fentanyl, and oxymorphone.

Recent trials primarily focus on the newer fentanyl products: oral transmucosal lozenges (Actiq, generic) and buccal tablets (Fentora). There is insufficient comparative evidence to directly compare the two formulations. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The two products cannot be switched at a 1:1 conversion due to the difference in bioavailability (for example, patients receiving 200 to 400 mcg of Actiq should start on 100 mcg of Fentora). A specific regimen is provided in Fentora labeling for converting from Actiq to Fentora (but not vice versa). From a safety standpoint, there is probably a significant potential for medication errors related to this conversion.

vi) Clinical evidence in neuropathic pain

Authors of a systematic review of double-blinded, placebo-controlled trials in neuropathic pain conditions [Finnerup *et al.*, 2005] attempted to use numbers-needed-to-treat (NNTs) to achieve one patient with 50% pain relief and numbers-needed-to-harm (NNHs) for one patient to drop out due to adverse effects to construct a treatment algorithm for neuropathic pain. The systematic review included 11 trials comparing opioids (morphine, oxycodone, methadone, or tramadol) to placebo. These trials showed evidence of efficacy for morphine in post-herpetic neuralgia and mixed neuropathic pain; oxycodone and tramadol in post-herpetic neuralgia and polyneuropathy, and methadone in post-herpetic neuralgia.

Authors concluded that if the proposed algorithm was based solely on NNTs for pain relief, it should place TCAs first, followed by opioids or gabapentin/pregabalin. However, taking into account quality of life measures and NNHs, the authors proposed an algorithm placing opioids as third-line therapy, following TCAs and gabapentin/pregabalin. A 2005 meta-analysis [Eisenberg *et al.*, 2005] that included most of the same trials but excluded tramadol found overall efficacy for opioids in neuropathic pain, compared to placebo.

Overall, while there is evidence that opioids are effective for neuropathic pain, there is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

b) *Acute pain*

The clinical review divided acute pain into two types, based on etiology: non-specific pain (e.g., low back, neck, shoulder, arm, or extremity pain) and post-operative pain.

Data in acute pain consist primarily of a plethora of very small, short-term (including single-dose) trials, most commonly in patients with post-op pain, and meta-analyses of these trials. There is little clinical evidence specifically addressing non-specific acute pain.

The most coherent approach to making sense of the available data appears to be the Oxford League Table of Analgesic Efficacy, a resource maintained by the evidence-based medicine journal/site Bandolier. The "League Table" aggregates data from randomized, double-blind, single-dose studies in patients with moderate to severe pain, using the NNT to achieve at least 50% pain relief over 4 to 6 hours as a common measure. Despite reliability issues (confidence intervals are broad for agents with relatively small datasets and probably unreliable for datasets representing fewer than 250 patients), some tentative conclusions can be drawn:

- For the combination agents, the League table generally supports the common perception of relative efficacy (oxycodone/APAP > hydrocodone/APAP > codeine or propoxyphene/APAP).
- Overall, both opioid combination agents and tramadol compare relatively poorly with NSAIDs.

Sources addressing agents not included in the League table did not add substantially to available data. One double-blind RCT [White *et al.*, 1997] found similar efficacy with hydrocodone 7.5 mg/APAP 750 mg and ketorolac 10 mg given every 6 hours for up to 3 days following tubal ligation (although neither agent was regarded by authors as very effective). Ketorolac appeared to be more tolerable. A Cochrane review of 16 poor quality studies [Elbourne and Wiseman, 2006] comparing IM meperidine to tramadol or pentazocine concluded there was insufficient evidence to evaluate comparable efficacy and safety. More vomiting and drowsiness was noted with meperidine.

The VA/DoD guideline for postoperative pain draws few specific conclusions, but does advise against use of meperidine.

Overall, there is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

c) *Efficacy conclusion*

The DoD P&T Committee concluded that:

a) All of the reviewed narcotic analgesics appear to be effective at providing analgesia when used in equipotent dosing. There is insufficient evidence to conclude that there are differences in efficacy between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both Avinza and Kadian capsules can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. There is insufficient evidence to conclude that there are differences in efficacy between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain. Trials focusing on the newer IR fentanyl products—oral transmucosal lozenges and buccal tablets—do not supply sufficient evidence to directly compare efficacy. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The lack of a 1:1 conversion between the two formulations may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first-line treatment for the treatment of neuropathic pain. There is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

2) Safety and Tolerability

a) General adverse effects

Narcotic analgesics are associated with an increased risk of nausea, vomiting and constipation. Other prominent adverse effects include mood changes (dysphoria, euphoria), somnolence, urinary retention (associated with increased sphincter tone), and urticaria/pruritis (associated with histamine

release). Respiratory depression is uncommon but potentially serious. Death secondary to opiate overdose is nearly always due to respiratory depression. When these agents are appropriately titrated, the risk of severe respiratory depression is generally small, as tolerance rapidly develops to this effect.

A decrease in seizure threshold occurs with the use of all narcotics and is of particular concern when these medications are given with other agents that lower seizure threshold or used in patients predisposed to seizure.

Codeine is often associated with gastrointestinal intolerance, which some patients incorrectly identify as an allergic reaction. True allergy to opiate agonists is uncommon. Narcotic analgesics may also decrease or inhibit salivary flow, contributing to oral/dental problems.

b) Drug-specific adverse effects

Meperidine – Neurotoxicity (anxiety, tremors, myoclonus, and generalized seizures) has been observed with repeated use of meperidine due to accumulation of a metabolite, normeperidine, which functions as a CNS excitotoxin. Patients using meperidine for more than two days, with pre-existing renal impairment, sickle-cell disease, or CNS disease, or receiving meperidine doses greater than 600 mg/24 hours are at particularly high risk for normeperidine toxicity. Use in children is not recommended.

Propoxyphene – Like meperidine, propoxyphene has CNS-excitatory metabolites and can cause CNS disturbances including seizure when administered in high doses, especially in patients with renal disease. Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths (many of them in patients with histories of emotional disturbance, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs). The consumer watchdog group Public Citizen petitioned the FDA in February 2006 to phase out propoxyphene from the U.S. market. Propoxyphene overdoses can be more difficult to reverse than with other opioids. Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. It is one-half to two-thirds as potent an analgesic as codeine.

Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

Tramadol – Doses of tramadol are limited by its association with an increased risk of seizure at higher than recommended doses. Per labeling, total dose should not exceed 300 mg of tramadol per day for the ER tablets (Ultram ER) and tramadol/APAP combination (Ultracet, generics), or 400 mg per day for tramadol IR tablets (Ultram, generics). Tramadol may increase seizure risk in

patients with a history of seizures, conditions with a recognized risk of seizure, or taking other medications that increase seizure risk.

Oral transmucosal and buccal fentanyl citrate are IR, high potency products indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and tolerant of opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who have been taking morphine 60 mg/day or more, transdermal fentanyl 50 mcg/h, or an equianalgesic dose of another opioid for a week or longer. These products should not be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. They are contraindicated in the management of acute or postoperative pain. Patients requiring more than four doses per day should have their maintenance analgesic reevaluated; use of round-the-clock oral transmucosal or buccal fentanyl citrate is not recommended.

Transdermal fentanyl is indicated for management of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. It should not be used for management of acute pain or short periods of opioid analgesia; post-op pain, including outpatient/day surgeries; mild pain; or intermittent pain. The DoD P&T Committee agreed in November 2006 that a PA was needed for transdermal fentanyl; the recommendation was approved by the Director, TMA in January 2007. Please see the November 2006 DoD P&T minutes for more information.

c) *Potential for abuse*

Numerous factors determine how and whether a drug is abused. It is generally accepted that rapidly acting medications (or ER dosage systems that can be compromised to cause drug to become rapidly available) are more prone to abuse than slow-acting or ER medications. Factors such as availability, local market conditions, drug popularity, and drug abuse culture may very greatly among geographic areas. Prescriptions for C-III to C-V controlled medications can generally be phoned in to pharmacies, written with refills, and are not tracked in statewide databases. This makes them easier to obtain through fraudulent activity (e.g., forging prescriptions). Prescriptions for C-II controlled medications, which have restrictions on telephone orders, cannot be refilled, and are usually tracked at the state level, are more difficult to obtain but are also more desirable to addicts due to their higher potency. Clearly there are differences among narcotic analgesics with regard to these factors; however, there were no data supporting differences in potential for abuse among like medications (for example, comparing the various long-acting high potency formulations) that the P&T Committee considered useful for making formulary recommendations.

d) Drug interactions

A large number of medications may interact with the narcotic analgesics. In general, these drug interactions are relatively similar for all of the drugs in this class and do not suggest that any particular medication offers a substantially higher potential for drug interactions. One unique consideration arises due to the dual mechanism of action of tramadol, leading to potential interactions (including increased risk of seizures or serotonin syndrome) with other medications that increase levels of serotonin and/or norepinephrine (e.g., MAOIs and selective serotonin reuptake inhibitors [SSRIs]). Another is the potential for a lethal hyperpyrexic syndrome with delirium if meperidine is administered to patients receiving MAOIs; this combination is contraindicated.

e) Special populations

There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route (e.g., as a transdermal patch, nasal spray, buccal tablet, transmucosal lozenge, or rectal suppository). The available narcotic analgesics offer various formulations that meet these needs (see Table 1).

3) Provider Opinion

The P&T Committee reviewed survey responses from 342 MHS healthcare providers with experience in prescribing narcotic analgesics for the treatment of pain. Responders represented more than 40 specialties (including a number of dental specialties), reflecting the ubiquity of use of the narcotic analgesics in clinical practice; however, the majority of responders were from Family Practice, Internal Medicine, and General Surgery. Overall, providers emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/acetaminophen combination products.

The P&T Committee also reviewed comments from MTF pharmacists regarding the ability of their facilities to accommodate additional controlled substances if placed on the BCF, which would require additional vault space and increase administrative burden (i.e., performing narcotic counts) for MTFs that did not already have the additional medications on formulary. Many pharmacists indicated that centralized contracting for “pre-packed” products in commonly-

dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

4) Clinical Coverage Considerations

The issue of clinical coverage, or "how many agents do we need on formulary to meet the majority of patients' needs," is dependent on multiple factors, including the efficacy, safety, and tolerability of individual agents for the treatment of conditions in which they are used, the needs of specific subpopulations, how interchangeable the medications are, the degree of intra-patient variability, and whether or not patients failing one agent (due to lack of efficacy, adverse effects, or hypersensitivity) typically respond to or tolerate another. In the case of the narcotic analgesics, several factors support availability of multiple agents and formulations.

- There is evidence that patients failing one narcotic analgesic due to lack of efficacy may respond better to another.
- Patients allergic to medications in one chemical class may be able to tolerate another without cross-sensitivity (i.e., may be able to take a phenylheptane [e.g., methadone] if allergic to a phenanthrene [e.g., morphine]).
- As with other pain medications, there is substantial intra-patient variability in response. Rotation of different narcotic analgesics has been proposed as a strategy to increase efficacy and decrease adverse effects, although clinical data are limited.
- Alternative formulations (e.g., liquids, suppositories, or patches) are needed in some patient populations. Long-acting products may be desirable not only for convenience, but to provide more blood concentrations and reduce the number of episodes of breakthrough pain.
- Utilization of these agents spreads across the entire population and touches virtually every disease state and professional specialty. Differences in clinical practice exist both locally and by specialty (e.g., products typically used in dental practice).

5) Narcotic Analgesics – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products

offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between 12-hour (e.g., MS Contin and generics) and 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) There is insufficient evidence to support efficacy differences between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges and buccal tablets). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

h) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

i) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days, in patients with renal impairment, sickle-cell disease, or CNS disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

j) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of

falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

k) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data supporting differences in potential for abuse among like medications (e.g., high potency, long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

l) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., MAOIs, SSRIs); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

m) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

n) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

o) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for “pre-packed” products in commonly-dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

p) Clinical coverage considerations support a broad array of formulary agents and formulations.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. Narcotic Analgesics – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the agents in the narcotic analgesic therapeutic class in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analyses (CMAs) were conducted for four subclasses of the narcotic analgesics, which differed slightly from the categories used during the clinical review: (1) long-acting high potency single analgesic agents; (2) short-acting high potency single analgesic agents; (3) low potency single analgesic agents; and (4) combination products. The conclusion of the relative clinical effectiveness evaluation was that there was insufficient evidence to suggest that the narcotic analgesics differed within the defined subclasses (long-acting high potency agents, short-acting high potency agents, low potency agents, and combination products) in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of pain. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the agents based on their weighted average cost per equianalgesic dose.

The results of the CMA for the high potency long-acting single analgesic agents showed that the 12-hour morphine sulfate ER product (MS Contin, generics) was the most cost effective agent. This result was anticipated since this product is generically available at a significantly discounted cost relative to brand name MS Contin. The other long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza), fentanyl patch, oxycodone ER, and oxymorphone ER—were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin, generics). Two of these products, fentanyl patch and oxycodone ER only recently became generically available. The cost of these generics is only slightly lower than their respective brand name products. The other three long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza) and oxymorphone ER—are brand-only products. There was no substantial difference in cost effectiveness between Kadian and Avinza.

The results of the CMA for the high potency short-acting single analgesic agents showed that morphine sulfate IR and oxycodone IR had similar relative cost effectiveness and were the most cost effective agents. Once again, this result was anticipated since morphine sulfate IR and oxycodone IR are now generically available at a significantly discounted cost relative to the their respective brand name products. The other two agents, fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges, were 40-fold the cost of the two most cost effective agents. Fentanyl citrate transmucosal lozenges only recently became generically available. There was no substantial difference in cost effectiveness between the two fentanyl citrate products (Fentora versus Actiq or its generic equivalent).

The results of the CMA for the low potency single analgesic agents showed that tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available.

The CMA for the combination agents showed that the agents within this generic-dominated class were all similar in terms of relative cost effectiveness.

The P&T Committee's discussion primarily focused on the relative clinical and cost effectiveness of the high potency long-acting and high potency short-acting single analgesic agents. The general consensus of the P&T Committee was that the UF should provide a broad array of these agents sufficient to meet the clinical needs of the DoD population. The P&T Committee made the following conclusions for each of these two subclasses:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), these agents should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population. This conclusion was based on the following factors:

    a. The 24-hour ER morphine products (Kadian and Avinza) provide more consistent levels of medication throughout a 24-hour period, which may reduce the number and/or severity of breakthrough pain episodes. Both products can be sprinkled on food to ease administration for patients who cannot swallow oral solid dosage forms. There was no substantial difference in cost effectiveness between Kadian and Avinza.

    b. Oxycodone ER provides an alternative for patients who cannot tolerate morphine sulfate.

    c. Transdermal fentanyl provides a unique dosage form for patients who are unable to swallow.

    d. Oxymorphone ER provides an additional long-acting oral alternative for patients who cannot tolerate morphine sulfate or oxycodone. The place of oxymorphone in therapy relative to other long-acting narcotic analgesics with much longer periods of clinical experience is not yet clear.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

Cost Effectiveness Conclusion

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they have unique clinical

advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

The P&T Committee agreed (14 for, 0 opposed, 1 abstained, 2 absent) with the relative cost effectiveness analysis of the narcotic analgesic agents.

C. Narcotic Analgesics – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER tablets be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established quantity limits for fentanyl transmucosal lozenges, recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

D. Narcotic Analgesics – MN Criteria

Based on the clinical evaluation for tramadol ER and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for tramadol ER:

1) Use of formulary alternatives is contraindicated.

2) The patient previously responded to tramadol ER and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee did not agree that other MN criteria were likely to apply, given the UF status of tramadol IR.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. Narcotic Analgesics – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 6500 patients [~1.5%] out of approximately 437,000 unique utilizers at all three points of

service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tramadol ER on their local formularies. MTFs will be able to fill non-formulary requests for this medication only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary narcotic analgesic written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Narcotic Analgesics – BCF Review and Recommendation

The P&T Committee considered the BCF status of the narcotic analgesics. Currently the only narcotic analgesic agents on the BCF are the 15 mg, 30 mg, and 60 mg strengths of morphine sulfate ER (MS Contin, generics); codeine/APAP oral (formulations not specified), and oxycodone/APAP 5/325 mg or 5/500 mg tablets. In addition to the medications already on the BCF, the P&T Committee agreed that morphine sulfate IR 15 and 30 mg and tramadol IR 50 mg should be added to the BCF and that the listings for hydrocodone/APAP and codeine/APAP should be clarified to specify the most commonly used and clinically necessary formulations and strengths (hydrocodone / APAP 5/500 mg; codeine/APAP 30/300 mg, and codeine/APAP elixir 12/120 mg per 5 mL). All of these drugs are cost effective, widely used agents in the MTF setting.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the following agents be designated as the BCF selections in this class: morphine sulfate ER 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/APAP 5/325 mg; hydrocodone/ APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/APAP elixir 12/120 mg per 5 mL; and tramadol IR 50 mg.

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents. Based on chemical structure and mechanism of action, the drug class was divided into seven categories as outlined in Table 2. The seven categories include ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors; alpha 2 adrenergics; adrenergics; cholinergics; and cholinesterase inhibitors. The glaucoma drug class accounted for $51.1 million in MHS expenditures in FY 2006, and is ranked #34 in terms of total expenditures during that time period.

A. Ophthalmic Glaucoma Agents – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical

review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 2: Ophthalmic Glaucoma Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Prostaglandin Analogs	Bimatoprost Latanoprost Travoprost	Lumigan Xalatan Travatan; Travatan Z
Beta Blockers	Betaxolol Carteolol Levobunolol Metipranolol Timolol maleate solution Timolol maleate gel-forming solution Timolol maleate with potassium sorbate Timolol hemihydrate	Betoptic, generics; Betoptic-S Ocupress, generics Betagan, generics Optipranolol, generics Timoptic, generics Timoptic XE, generics Istalol Betimol
Carbonic Anhydrase Inhibitor; Combination Drug	Brinzolamide Dorzolamide Dorzolamide / timolol	Azopt Trusopt Cosopt
Alpha 2 adrenergics	Brimonidine BAK 0.2% Brimonidine Purite 0.15%/ 0.1% Apraclonidine	Generic (Alphagan brand discontinued) Alphagan P Iopidine
Adrenergics	Dipivefrin	Propine, generics
Cholinergics (miotics)	Acetylcholine Carbachol Pilocarpine	Miochol-E Isopto Carbachol Pilocar, generics; Pilopine HS gel
Cholinesterase Inhibitors	Echothiophate	Phospholine iodide

1) Efficacy Measures

The primary outcome measure used to assess efficacy of the glaucoma drugs is the change in intraocular pressure (IOP) as compared to baseline, expressed as an absolute value in mm Hg or as a relative percentage change from baseline.

2) Efficacy

a) Prostaglandin analogs

i) Products – The prostaglandins available on the market include bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan). These three products contain benzalkonium chloride (BAK) as a preservative, which has been associated with local ocular irritation. Travoprost is also available with a non-BAK preservative under the trade name of Travatan Z. None of the products are available in generic formulations.

ii) Meta-analyses – The efficacy of the ophthalmic prostaglandin analogs was evaluated in two meta-analyses. At peak levels, the mean differences from baseline IOP were similar; -33% (95% CI -29% to -27%) with bimatoprost,

-28% (95% CI -30% to -26%) with latanoprost, and -29% (95% CI -32% to -25%) with travoprost [Van der Valk *et al.*, 2005].

Ni Li *et al.* in 2006 found no difference in the IOP lowering effects when travoprost was compared to bimatoprost (weighted mean difference 0.08, 95% CI -0.62 to 0.79; p=0.8), or to latanoprost (weighted mean difference 0.57, 95% CI -1.18 to 0.04; p = 0.07). The IOP lowering efficacy of bimatoprost was not directly compared to latanoprost.

iii) Head-to-head trials – Two RCTs that evaluated the prostaglandin analogs in a head-to-head manner did not find significant differences in the efficacy of the drugs. Parrish *et al.* in 2003 found no difference among all comparison groups (p = 0.128), while Orzalesi *et al.* in 2006 reported that the performance of all three drugs was statistically identical within the 1.5 mmHg power of the trial.

iii) Racial differences in efficacy – Travoprost was more effective than latanoprost at lowering IOP in African Americans than non-African Americans in one sub-analysis [Netland *et al.*, 2001]. The difference of up to 1.5 mm Hg was statistically significant (p = 0.04) in favor of travoprost. However, this was a post-hoc analysis that was not prospectively designed to evaluate racial differences in efficacy.

No significant differences between bimatoprost and travoprost in mean IOP-lowering were found in one prospectively designed trial involving ninety-four African American patients [Noecker *et al.*, 2006]. Both drugs resulted in a statistically significant reduction from baseline IOP at all study visits ($p < 0.001$). There were no statistically significant between-group differences in IOP-lowering ($p \geq 0.130$).

b) Beta blockers

i) Products – Six ophthalmic beta blockers are included in the class; one β1 selective product, betaxolol (Betoptic-S, Betoptic); and five non-selective products, levobunolol (Betagan), metipranolol (OptiPranolol), timolol hemihydrate (Betimol), timolol maleate (Timoptic, Istalol, Timoptic Ocudose and Timoptic XE, a gel-forming solution), and carteolol (Ocupress).

ii) Generics – Several beta blockers are available in generic formulations, with the exception of betaxolol suspension 0.25% (Betoptic-S), timolol hemihydrate (Betimol), the branded timolol maleate product Istalol, and preservative free unit dose timolol maleate (Timoptic Ocudose).

iii) Timolol – Timolol was the first beta blocker marketed and is the gold standard to which other ophthalmic glaucoma agents are compared. On average, timolol reduces IOP by 20% to 35%. Several different formulations and salts are available:

- *Timolol maleate solution (Timoptic, generics) versus timolol maleate gel-forming solution* – Timolol maleate solution requires twice daily

dosing. Timolol maleate gel-forming solution is dosed once daily, and potentially has increased ocular penetration and duration of action compared to the solution, but causes transient blurred vision. One study comparing the solution with the gel-forming solution found no difference in IOP-lowering from baseline; both products lowered IOP by 30% to 31%.

- *Timolol hemihydrate* – The timolol hemihydrate salt theoretically enhances ocular drug availability, due to increased solubility compared to timolol maleate. The hemihydrate formulation is dosed twice daily, as is timolol maleate. Two comparative studies of timolol hemihydrate with timolol maleate solution or timolol maleate gel-forming solution showed similar reductions in IOP from baseline by about 22%. One study [Mundorf *et al.*, 1998] found there was no change in IOP after three months when patients previously receiving timolol maleate solution were switched to timolol hemihydrate.
- *Timolol maleate (Istalol)* – The timolol maleate branded product Istalol is dosed once daily. Potassium sorbate is incorporated into the formulation, which purportedly enhances ocular penetration into the eye. However, a clinical trial comparing Istalol to timolol maleate (Timoptic, generics) dosed twice daily demonstrated no efficacy differences between the products, both drugs reduced IOP by 23% to 24% [Mundorf *et al.*, 2004].

iv) Levobunolol, metipranolol, carteolol – Comparative trials with the non-selective beta blockers levobunolol, metipranolol, and carteolol each with timolol maleate (Timoptic, generics) show similar reductions in IOP.

vi) Betaxolol – Betaxolol is the sole β_1 selective ophthalmic beta blocker. It is available in two strengths, a 0.25% suspension (Betoptic-S) that is not available in a generic formulation, and a 0.5% solution (Betoptic, generics). Clinical trial data suggest that timolol maleate may decrease IOP to a greater extent than betaxolol. Due to betaxolol's β_1 selectivity, patients with respiratory or reactive airway diseases may not experience adverse pulmonary effects seen with non-selective beta blockers. However, there is only one published study enrolling nine subjects demonstrating a lack of adverse effect on pulmonary function tests.

c) Carbonic anhydrase inhibitors; combinations with beta blockers

i) Products – The ophthalmic carbonic anhydrase inhibitors include brinzolamide (Azopt), and dorzolamide (Trusopt). The branded product Cosopt consists of dorzolamide and timolol maleate and is the only combination glaucoma product marketed. Generic formulations of the three products are not available. The carbonic anhydrase inhibitors are used in patients with contraindications to other glaucoma drugs, and can be used concomitantly with other drugs that lower IOP. Brinzolamide and dorzolamide both decrease intraocular pressure by 15%-26%.

ii) Meta-analysis – One meta-analysis included an indirect comparison of brinzolamide and dorzolamide. Both drugs significantly reduced IOP, compared with placebo. At trough levels, the mean differences from baseline IOP were similar; -17% (95% CI -19% to -15%) for both drugs [Van der Valk *et al.*, 2005].

Head-to-head trials – One randomized trial reported similar reductions in IOP with brinzolamideand dorzolamide (-17% to -20% for both), compared to increases in IOP of 8% to 19% with placebo [Sall *et al.*, 2000]. When brinzolamide and dorzolamide were given with timolol maleate, similar IOP reductions were also seen (-14% to -21% for both) [Michaud *et al.*, 2001]. Similar absolute reductions in IOP of 0.1 to 0.3 mm Hg were reported with brinzolamide and dorzolamide when the carbonic anhydrase inhibitor was added on to a regimen of latanoprost and timolol (Timoptic, generics) [Tsukamoto *et al.*, 2005].

iii) Dorzolamide/timolol (Cosopt) – Clinical trials sponsored by the manufacturer lasting 3 to 15 months found the combination of dorzolamide with timolol produced similar reductions in IOP as the two separate components administered together. The net effect of administering the Cosopt combination is an absolute IOP reduction of 3-4 mm Hg below that seen with timolol (Timoptic, generics).

d) Alpha 2 adrenergics

i) Products – The alpha 2 adrenergic agents include the parent compounds of apraclonidine (Iopidine) and brimonidine. Brimonidine is available in three formulations: a 0.2% concentration with BAK as a preservative (available only as a generic, as the proprietary product has been discontinued); a 0.15% solution with purite as a preservative (Alphagan P), and a 0.1% solution with purite as a preservative (also called Alphagan P). Apraclonidine and brimonidine reduce intraocular pressure by 18% to 27% two to five hours after dosing and by 10% at 8 to 12 hours after administration.

ii) FDA Indications – There are differences in the FDA-approved indications for apraclonidine and brimonidine. All formulations of brimonidine BAK 0.2% (generic) and brimonidine purite 0.15% and 0.1% (Alphagan P) are indicated to reduce IOP in patients with glaucoma. Apraclonidine is approved for use following laser procedures to control post-surgical IOP elevations (1% concentration), or for short-term use in patients receiving maximally tolerated medical therapy who require additional IOP reductions prior to surgery (0.5% concentration).

iii) Apraclonidine – Apraclonidine is primarily used short-term, as it is associated with tachyphylaxis and diminished intraocular pressure lowering effect over time. DoD utilization of apraclonidine represents a small percentage of overall alpha 2 adrenergic drug use (0.5%).

iv) Apraclonidine versus brimonidine 0.2% BAK – Head-to-head studies of brimonidine BAK 0.2% and apraclonidine demonstrated similar intraocular

pressure lowering effects, both in patients with glaucoma, and in laser surgery. Both agents lower intraocular pressure by 17 to 26% in this setting.

v) Brimonidine – One meta-analysis reported that brimonidine reduced intraocular pressure by 25% at peak and 18% at trough, but to a lesser extent than the prostaglandins (25% to 35%) [Van der Valk *et al.*, 2005].

Brimonidine formulations – Two head-to-head trials comparing brimonidine BAK 0.2% formulation (generic) with brimonidine purite 0.15% (Alphagan P) did not show differences in IOP lowering [Katz *et al.*, 2002; Mundorf *et al.*, 2003]. One comparative trial with brimonidine purite 0.1% (Alphagan P) reported similar efficacy with brimonidine BAK 0.2% (generic), but few details were provided [package insert]. Product labeling states that the brimonidine purite 0.15% (Alphagan P) and brimonidine purite 0.1% (Alphagan P) both lower IOP by 2-6 mmHg; no corresponding percentage reduction in intraocular pressure was provided.

e) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Products – Dipivefrin (Propine, generic) is the only ophthalmic adrenergic, and echothiophate (Phospholine iodide) is the only ophthalmic cholinesterase inhibitor. The cholinergics include acetylcholine (Miochol-E), carbachol (Isopto Carbachol), and pilocarpine gel (Pilopine HS) and pilocarpine solution (Pilocar, generics). The adrenergics, cholinergics, and cholinesterase inhibitors were introduced in the early 1980s, and were the first agents used to treat glaucoma, but have been replaced by newer therapies, due to adverse effects. They are now third-line treatments for glaucoma, but do fulfill unique niches in therapy.

ii) Dipivefrin – Dipivefrin is a pro-drug that has improved lipophilicity and enhanced corneal penetration compared to the parent compound epinephrine. IOP reduction with dipivefrin ranges from 15% to 25%.

iii) Cholinergics – The direct-acting cholinergics or miotics are used for glaucoma to decrease IOP via increased aqueous outflow, or are used to induce miosis during surgery. Acetylcholine, carbachol and pilocarpine solution are all dosed four times daily; only pilocarpine solution is available generically.

Acetylcholine – Acetylcholine is used intraocularly to constrict the pupil during cataract surgery, or after placement of the intraocular lens following cataract removal.

Carbachol – Carbachol has two mechanisms to decrease IOP; it directly stimulates muscarinic receptors in the eye, and indirectly inhibits acetylcholinesterase.

Pilocarpine – Pilocarpine lowers IOP by 22% to 30%. It is dosed four times daily in the treatment of open-angle glaucoma. In acute angle closure glaucoma, pilocarpine is used as monotherapy or in combination with other cholinergic agents or with a carbonic anhydrase inhibitor to relieve IOP prior to ocular surgery. Pilocarpine gel is a sustained release formulation

that is applied at bedtime to provide 24-hour control of IOP; pilocarpine gel reduces the adverse effects of myopia.

iv) Echothiophate – Echothiophate is dosed twice daily for glaucoma. It has a role for the treatment of aphakia or pseudophakia (patients with their lens replaced by artificial lens). The drug is poorly absorbed due to its quaternary structure, but has similar IOP reductions as pilocarpine.

3) Safety / tolerability

a) Prostaglandin analogs

i) Serious adverse events – Overall the ophthalmic prostaglandins have a low incidence of systemic adverse effects, which has contributed to their use as first-line therapy for glaucoma.

ii) Minor adverse events

- *Hyperemia* is the most common minor adverse event reported with the ophthalmic prostaglandins. A comparison of package insert data shows a higher incidence of hyperemia with bimatoprost (15-45%) and travoprost (30-50%), as compared to latanoprost (5-15%). In one head-to-head trial, hyperemia occurred in 69% of patients receiving bimatoprost, 58% of travoprost-treated patients, and 47% of latanoprost-treated patients [Parrish *et al.*, 2003]. Significantly fewer patients experienced an ocular adverse event with latanoprost in this trial. Hyperemia appears to be more of a cosmetic issue and is noted to generally be mild in severity and transient in nature.
- *Increased pigmentation* occurs more frequently with latanoprost (5-15%) than either bimatoprost (1-3%) or travoprost (1-4%). The pigmentation changes may be permanent.
- *Preservatives (Travatan versus Travatan Z)* – Products with preservatives that do not contain BAK are purported to have a favorable adverse event profile over products with BAK-based preservatives. A randomized trial in 700 patients evaluated the adverse events of the BAK-containing travoprost product (Travatan) with the non-BAK preservative formulation (Travatan Z). Hyperemia occurred in 9% of patients receiving Travatan, compared to 6.4% with Travatan Z (no p value provided) [Lewis 2007]. The adverse events in this trial were not serious and did not interrupt treatment.

iii) Drug discontinuations due to adverse effects

The prostaglandins are well tolerated. Discontinuation rates noted in package labeling due to conjunctival hyperemia were 3% for both travoprost and bimatoprost, and <1% for latanoprost. The discontinuation rates due to adverse events in one head to head trial were 0.7% with travoprost, 1.4% with bimatoprost, and zero with latanoprost [Parrish *et al.*, 2003].

b) Beta blockers

i) Serious adverse events – As a class, the ophthalmic beta blockers are associated with systemic adverse effects that limit their use for glaucoma, including bradycardia, arrhythmia, cardiac block, congestive heart failure, and bronchospasm. Betaxolol is the only β1 selective ophthalmic beta blocker; however bronchospasm has occurred in patients with asthma and chronic obstructive pulmonary disease. Both selective and non-selective beta blockers are contraindicated for use in patients with severe cardiovascular disease including sinus bradycardia, second and third degree heart block, cardiogenic shock, or patients with overt cardiac failure.

ii) Minor adverse events – Local adverse events of the beta blockers include stinging, itching, redness and blurred vision, which may be due to the preservative and pH of the solutions. Overall, stinging is most commonly associated with betaxolol and metipranolol. Timoptic maleate gel-forming solution is associated with transient blurry vision due to its thick consistency upon instillation.

Timolol maleate (Istalol) – A higher incidence of burning and stinging was associated with the once daily branded formulation of timolol maleate (Istalol) compared to timolol maleate (Timoptic, generics) in one trial (41.6% versus 22.9%) [Mundorf *et al.*, 2004].

c) Carbonic anhydrase inhibitors; and combinations with beta blockers

i) Serious adverse events – Brinzolamide and dorzolamide both have similar contraindications (hypersensitivity to the individual components). Brinzolamide/timolol (Cosopt) contains precautions regarding pulmonary and cardiovascular function seen with other ophthalmic beta blockers, due to the timolol component. Rare effects with dorzolamide include altered cornea endothelial cell function, renal calculi, and thrombocytopenia.

ii) Minor adverse effects – The most common adverse effects of the ophthalmic carbonic anhydrase inhibitors include local burning and stinging upon drug instillation, and taste perversion. In head-to-head-trials comparing brinzolamide with dorzolamide, dorzolamide was associated with a higher incidence of burning/stinging (12-16% versus 2-3%). The higher incidence of ocular discomfort with dorzolamide may be due to the acidic pH of the product (5.6) versus the more physiologic pH of brinzolamide (7.5). However, the ocular discomfort with dorzolamide appears transient, lasts about 10 seconds, is characterized as mild and diminishes with continued therapy [Stewart *et al.*, 2004]. The incidence of taste perversion appears similar between the two products, based on head-to-head clinical trials.

iii) Discontinuations due to adverse effects – It is difficult to determine differences in tolerability between brinzolamideand dorzolamide, as only a few patients discontinued therapy due to adverse events in the head-to-head clinical trials.

d) Alpha 2 adrenergics

i) Serious adverse effects – Both apraclonidine and brimonidine are contraindicated in patients with hypersensitivity to the individual agents, patients taking clonidine, and patients taking MAOIs. The alpha 2 adrenergics as a class may reduce pulse and blood pressure. Apraclonidine penetrates the blood brain barrier to a lesser extent than brimonidine, and is less likely to reduce heart rate and blood pressure.

ii) Minor adverse effects – Overall, the alpha 2 adrenergics are associated with a relatively high incidence of minor adverse events, including fatigue and local allergic reactions, compared to other glaucoma drug classes. As a class, the alpha 2 adrenergic agents can cause ocular intolerance (allergy leading to conjunctival erythema and potential periorbital infection) in 13% to 36% of patients. Apraclonidine can cause dry nose and mouth and upper eyelid retraction, and follicular conjunctivitis has occurred frequently. Brimonidine has a higher incidence of dry mouth (33%) than apraclonidine, but is associated with less frequent ocular side effects.

iii) Brimonidine formulations –There are three concentrations of brimonidine marketed; a 0.2% concentration with BAK as a preservative, and two products (0.15% and 0.1%) containing a purite preservative. There is only limited data comparing the safety differences between the three products. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2%. A statistically significant 41% reduction in reports of allergic conjunctivitis, oral dryness, conjunctival hyperemia, and eye discharge with brimonidine purite 0.15% compared to brimonidine BAK 0.2% was found in one head-to-head trial, [Katz *et al.*, 2002], while another study noted no significant differences between the two drugs in the overall incidence of adverse events [Mundorf *et al.*, 2003)]. Indirect comparison of the trials does not suggest any difference in the incidence of discontinuation due to adverse drug reactions between the two agents.

Data from an unpublished study cited in product labeling found a significantly lower frequency of treatment-related adverse events with brimonidine purite 0.1% (Alphagan P) versus brimonidine BAK 0.2%. More patients (34%) discontinued treatment due to adverse events with brimonidine BAK 0.2% than with brimonidine purite 0.1% (21%).

e) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Dipivefrin – Today dipivefrin is rarely used due to adverse effects such as conjunctival hyperemia, hypersensitivity and ocular irritation. It is contra-indicated in patients with narrow-angle glaucoma, since any dilation of the pupil may predispose the patient to an exacerbation of closed-angle glaucoma.

ii) Cholinergics – Retinal detachment and tearing may occur if the cholinergic drugs are used in patients with pre-existing retinal disease. Miotics may

also cause angle closure in patients with narrow angle glaucoma due to increased resistance to aqueous flow from the posterior to the anterior eye chamber.

Acetylcholine – Safety concerns with acetylcholine include infrequent corneal edema, corneal clouding, and corneal decompensation. Major adverse events are rare, but include bradycardia, hypotension, flushing, breathing difficulties, and sweating.

Carbachol – Carbachol is more potent than pilocarpine, and can induce significant adverse effects. Transient stinging and burning, in addition to corneal clouding have been reported. Brow ache is the most frequent patient-reported adverse effect, due to stimulation of the ciliary muscle, which exerts a physical pull on the trabecular mesh network. Older patients with cataracts often complain of dimmed vision caused by miosis. Severe but rare systemic effects include headache, sweating, epigastric distress, nausea, vomiting, and diarrhea.

Pilocarpine – Pilocarpine is associated with miosis or accommodative spasm, which may cause blurred vision and night blindness. Long-term use is limited by loss of visual field, due to the decreased amount of light entering the eye. Systemic adverse effects include atrioventricular block and other cardiovascular effects.

iii) Echothiophate – Echothiophate frequently causes blurred vision, brow ache, eyelid fasisculation, and watery eyes. Rarely, burning or stinging has been reported. Rare but serious adverse effects are similar to those of the miotics, but also include punctul stenosis of the nasolacrimal system. Organo-phosphate pesticides should be used with caution, as echothiophate activity may increase, raising the potential for adverse effects.

4) Other Factors

a) Prostaglandin analogs

Storage and stability – Latanoprost requires refrigeration prior to opening, to maintain a 36-month shelf life; it does not require refrigeration once opened. Bimatoprost and travoprost (Travatan, Travatan Z) do not require refrigeration.

Special populations – There are no differences between the prostaglandin analogs in their pregnancy category rating (all are pregnancy category C) or labeling for pediatric use (none are FDA-approved).

b) Beta blockers

Special populations – The ophthalmic beta blockers are rated a pregnancy category C. Timolol crosses into breast milk, so it should be avoided in lactating women. Safety and efficacy of ophthalmic beta-blockers have not been established in pediatrics. The majority of published information in children has been with timolol maleate. Topical application of timolol 0.5% can cause cardiac blockade in infants younger than 2 years of age.

Frequency of dosing – Patient convenience is an advantage of once daily ophthalmic beta blockers, particularly if multiple ophthalmic drugs are required. The branded timolol maleate product Istalol, and timolol maleate gel-forming solution are dosed once daily.

c) Carbonic anhydrase inhibitors; combinations with beta blockers

Dosing dispenser – The dosing dispenser of dorzolamide is specifically designed to deliver a controlled pre-measured drop, and will not operate unless the instructions are followed correctly.

Patient convenience – The primary advantage of the combination of dorzolamide with timolol (Cosopt) is patient convenience in reducing the number of bottles and daily ophthalmic drops required, potentially improving compliance.

d) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Dipivefrin – The adrenergic dipivefrin still has a place in therapy as adjunctive therapy to beta blockers, pilocarpine and carbachol.

ii) Cholinergics – The cholinergics are usually reserved for patients who have not responded to other topical glaucoma treatments.

Pilocarpine – Pilocarpine is used to treat acute angle closure glaucoma and as a miotic during ocular surgery.

iii) Echothiophate – The cholinesterase inhibitor echothiophate has fallen out of favor, due to four times daily dosing, compared to newer agents.

Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) *Prostaglandin analogs* – Bimatoprost, latanoprost, and travoprost all decrease IOP from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-BAK preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP-lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate, levobunolol, metipranolol and carteolol appear similar, based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles. Betaxolol decreases IOP to a lesser

extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamideand dorzolamide appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however, burning and stinging upon instillation last 10 seconds, diminish over time, and have not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to a similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). Brimonidine purite 0.1% (Alphagan P) may have an improved safety and tolerability profile compared to brimonidine BAK 0.1% (generic), but the one supportive study has not been published in a peer-reviewed journal.

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin, the cholinergics acetylcholine and carbachol and the cholinesterase inhibitor echothiophate serve unique niches in therapy.

6) Based on clinical issues alone, there are no compelling reasons to classify any of the glaucoma drugs as non-formulary on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions state above.

B. Ophthalmic Glaucoma Agents – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the ophthalmic glaucoma agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The ophthalmic glaucoma agents were classified and compared within subgroups based on mechanism of action. The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the glaucoma medications differed within subclasses in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of glaucoma. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the weighted average cost per day of treatment for each drug product.

Results from the CMA of the prostaglandin subclass included three key findings: (1) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; (2) Latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and (3) an all on scenario (i.e., all three prostaglandin products included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

The results from the CMA of the topical beta-blockers showed that the majority of these products were cost effective. Only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the P&T Committee in determining which group of ophthalmic glaucoma agents would best meet the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusions stated above.

C. Ophthalmic Glaucoma Agents – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol (Betoptic, generics; Betoptic-S), carteolol, metipranolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution (Timoptic XE, generics), brimonidine (generics; Alphagan P), apraclonidine, dorzolamide, dorzolamide/timolol (Cosopt), dipivefrin (Propine), acetylcholine (Miochol-E), carbachol (Isopto Carbachol), pilocarpine (Pilopine HS gel; Pilocar, generics), echothiophate (Phospholine Iodide) be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate (Betimol), timolol maleate (Istalol) and brinzolamidebe classified as non-formulary under the UF.

D. Ophthalmic Glaucoma Agents – MN Criteria

Based on the clinical evaluation for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T

Committee recommended the following general MN criteria for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide:

1) Formulary alternatives are contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. Ophthalmic Glaucoma Agents – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 17,000 patients [15%] of approximately 111,000 unique utilizers at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary glaucoma agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Ophthalmic Glaucoma Agents – BCF Review and Recommendations – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5%; and pilocarpine.

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's disease and not depression. The three oral MAOI antidepressants were first introduced to

the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars spent in FY 2006 wresp, which amounts to less than 1% of total MHS expenditures for all antidepressant drug classes.

A. MAOI Antidepressants – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the MAOI antidepressant agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) Pharmacology

There are two MAOI enzymes. Inhibition of MAO-B enzyme in the CNS leads to decreased metabolism of norepinephrine, dopamine and serotonin. Inhibition of MAO-A enzyme in the gastrointestinal tract results in decreased catabolism of tyramine, which can increase blood pressure. Patients taking MAOI anti-depressants who do not restrict dietary sources of tyramine can potentially develop hypertensive crisis. Theoretically, administering an MAOI anti-depressant via the transdermal route would obviate the need for strict dietary precautions.

2) Efficacy for Atypical Depression and Major Depressive Disorder (MDD)

a) FDA-approved indications

The three oral MAOI antidepressants, isocarboxazid, phenelzine, and tranylcypromine, are FDA-approved to treat either atypical depression or MDD. The selegiline transdermal patch is indicated only for treatment of MDD.

b) Efficacy measures

The Hamilton Rating Scale for Depression (HAM-D) is the most widely used observer-rated scale that assesses the symptoms and severity of depression. In efficacy trials for the MAOI antidepressants, a 50% reduction in the HAM-D from baseline was considered a response to treatment. Remission refers to reduction in the HAM-D score below a specific cut-off score.

c) Efficacy of oral MAOI antidepressants

i) Meta-analysis – One meta-analysis [Thase *et al.*, 1995] evaluated 55 RCTs (published from 1959 through 1992) that focused on depressive disorders in adults in the outpatient setting. The trials evaluated the efficacy of isocarboxazid, phenelzine, and tranylcypromine.

There were no apparent differences in the overall efficacy between isocarboxazid (60% ± 7%), phenelzine (58% ± 4%), and tranylcypromine (53% ± 12%). Limitations to the meta-analysis included differences in trial methodologies and patient populations between trials and the fact that evaluated studies were from approximately 30 years ago.

ii) Head-to-head clinical trial – One head-to-head trial compared the efficacy of phenelzine and tranylcypromine in 77 inpatients with antidepressant-refractory depression [Birkenhager *et al.*, 2004]. A response to therapy occurred in 44% (17/39) of the patients receiving tranylcypromine, and 47 % (18/38) of the patients randomized to phenelzine (p=0.82). Only 18% (7/39) of the tranylcypromine-treated patients and 11% (4/38) of the phenelzine-treated patients met criteria for remission (p=0.52). This trial had limited power to detect a difference between the two drugs and was conducted in the inpatient setting.

d) Efficacy of transdermal selegiline

Three published placebo-controlled trials lasting six to eight weeks and one open-label trial lasting 52 weeks evaluate the efficacy of the transdermal selegiline formulation. There are no comparative trials evaluating efficacy differences between transdermal selegiline and any of the three oral MAOI antidepressant or other antidepressants (e.g., TCAs, SSRIs).

i) Placebo-controlled trials – In the first trial, a response to therapy occurred in 38% of patients receiving transdermal selegiline 6 mg/24 hr, compared to 23% receiving placebo (p=0.01); remission occurred in 23% of the patients treated with the patch compared to 11 % with placebo (p=0.05) [Bodkin *et al.*, 2002]. In the second trial, response rates ranged from 32% to 33% with transdermal selegiline 6 mg/24 hr, versus 21% to 30% with placebo [Amsterdam *et al.*, 2003]. In the third trial [Fieger *et al.*, 2006], the response rate was 40% with transdermal selegiline (flexible dosing up to 12 mg/24 hr) versus 30% with placebo (p value not significant)

ii) Open label extension trial – In an open label extension trial enrolling 600 patients who had previously responded to transdermal selegiline, 17% of patients randomized to the patch relapsed after one year, compared to 31% of placebo-treated patients (p=0.003).

e) Clinical efficacy conclusion

A meta-analysis comparing the three oral MAOIs reported similar overall efficacy rates of 58% with phenelzine, 60% with isocarboxazid, and 53% with tranylcypromine in the outpatient setting. One trial conducted in an inpatient population found no statistically significant difference between phenelzine and tranylcypromine in response or remission rates. For transdermal selegiline, three placebo controlled trials are available. The response rates with transdermal selegiline ranged from 30% to 40%, compared to 21% to 30% with placebo.

3) Safety and Tolerability

a) *Minor adverse events* – The most common adverse effects of the oral MAOI antidepressants are orthostatic hypotension, dizziness, edema, tremor, insomnia, mydriasis, and anorgasmia. There are no data to suggest that one oral MAOI antidepressant is more likely than another to be associated with minor adverse effects.

Mild to moderate local irritation at the application site occurred in 15% to 36% of patients receiving transdermal selegiline in the placebo controlled trials. As with the oral MAOI antidepressants, insomnia and orthostatic hypotension are also concerns, with higher incidences reported with the 9 mg/24 hr and 12 mg/24 hr strengths.

b) *Serious adverse events* – As a class, the MAOI antidepressants have the potential for causing serotonin syndrome when administered with other serotonergic drugs or when dietary precautions are not followed. Deaths have been reported with the oral MAOI antidepressants due to both drug-drug and drug-food interactions. The MAOI antidepressants are considered third-line agents due to their adverse effect profile. To date there have been no deaths or other life-threatening events including hypertensive crisis attributed to transdermal selegiline in the controlled setting of the clinical trials.

c) *Drug-food interactions* – Consumption of tyramine-containing foods (e.g., aged meats, aged cheeses) and beverages (e.g., non-pasteurized beers) while taking any MAOI may result in hypertensive crisis. The lowest dosage strength of transdermal selegiline (6 mg/24 hr) is the only dosage where dietary tyramine restrictions are not required in the product labeling. A tyramine-restricted diet is required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. Most patients are likely to require the higher strengths of transdermal selegiline for MDD.

d) *Drug-drug interactions* – As a class, the oral MAOI antidepressants are associated with several well known and clinically important drug-drug interactions. The same extensive list of drug-drug interactions also applies to transdermal selegiline. Concomitant use of any MAOI antidepressant, including transdermal selegiline, is contraindicated with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, cyclobenzaprine, carbamazepine, other MAOIs, SSRIs, and amphetamine derivatives.

e) *Withdrawal due to adverse events* – Differences in tolerability profiles between the three oral MAOI antidepressants are difficult to determine, as the available clinical trials used less rigorous study design than is standard today.

In the three short-term (6- to 8-week) placebo controlled trials evaluating transdermal selegiline, 6% (23/370) of patients randomized to the patch discontinued therapy due to an adverse event, compared to 4% (16/373) of subjects in the placebo groups. Application site reactions were the most common reason for discontinuation. In the 52-week open label trial,

discontinuation rates due to application site reactions were 15% with transdermal selegiline versus 4% with placebo.

f) Safety and tolerability conclusion – The MAOI antidepressants as a class are associated with several serious adverse events. Hypertensive crisis and risk of death due to dietary and drug-drug interactions are well-publicized. In the placebo controlled trials with transdermal selegiline, a high incidence of local patch irritation was reported. Dietary restrictions are required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. There are no head-to-head trials comparing the safety and tolerability profiles of transdermal selegiline versus the oral MAOIs.

4) Other factors

a) Available dosage formulations – Transdermal selegiline is the only MAOI antidepressant available in a non-oral dosage formulation. Transdermal selegiline would be preferred over the oral MAOI antidepressants in patients with dysphagia.

b) Dosing frequency – Transdermal selegiline and tranylcypromine are the only MAOI antidepressants that are dosed once daily. Isocarboxazid and phenelzine require dosing twice to three times daily.

c) Potential for off-label uses – The oral MAOI antidepressants have many off-label uses other than depression, including panic disorder and social anxiety disorder. Oral selegiline is currently used in conjunction with carbidopa-levodopa in Parkinson's Disease. Transdermal selegiline is currently undergoing Phase II trials to evaluate efficacy for depression in patients with Parkinson's Disease, but no peer-reviewed studies have been published.

d) Pregnancy – The oral MAOI antidepressants and transdermal selegiline are contraindicated for use during pregnancy; however, there are published reports of the use of phenelzine and tranylcypromine in pregnant patients with severe depression.

e) Pediatrics – The three oral MAOI antidepressants and transdermal selegiline are not approved for use in children younger than 16 years of age.

f) Other factors conclusion – There are only minor differences in other factors for the MAOIs, including dosing frequency, availability of non-oral dosage formulations, and potential for off-label uses.

MAOI Antidepressant Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.

2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from tyramine.

3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.

4) Overall, response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.

5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.

6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hr). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOIs (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the Uniform Formulary.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. MAOI Antidepressants – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the MAOI antidepressants in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e) (2). Given the overall clinical conclusion that the agents within the MAOI class have similar relative clinical effectiveness, a CMA was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Results of the CMA for the MAOI class showed that:

1) Among the oral agents, phenelzine was the most cost effective agent, followed closely by tranylcypromine and isocarboxazid.

2) Transdermal selegiline was the least cost effective MAOI for the treatment of depression. The weighted average cost per day of treatment with transdermal selegiline was four-fold higher than the most costly oral MAOI, isocarboxazid.

Cost Effectiveness Conclusion

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

C. MAOI Antidepressants – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine, tranylcypromine and isocarboxazid be maintained as formulary on the UF and that transdermal selegiline be classified as non-formulary under the UF.

D. MAOI Antidepressants – MN Criteria

Based on the clinical evaluation for transdermal selegiline and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for transdermal selegiline:

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

4) The patient previously responded to a *non-formulary* pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

5) No formulary alternative is available.

The P&T Committee noted that criterion #5 would only apply to patients unable to take oral medications.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. MAOI Antidepressants – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The

implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have transdermal selegiline on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary MAOI antidepressant agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. MAOI Antidepressant – ECF Review and Recommendations

The P&T Committee had previously determined at the November 2006 P&T Committee meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that phenelzine be classified as the ECF agent. Phenelzine was determined to be the most cost effective MAOI and currently has the greatest utilization across the MHS.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend phenelzine be classified as the ECF agent.

10. CLASS OVERVIEWS

Portions of the clinical reviews for the ophthalmic non-steroidal anti-inflammatory agents (Ophthalmic NSAIDs) and erythropoiesis stimulating agents (ESAs) were presented to the P&T Committee.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the May 2007 or August 2007 meetings; no action is necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1430 hours on 14 February 2007. The next meeting will be 13-15 May 2007.

_____//signed//_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	Pending approval	Pending approval
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	Pending approval	Pending approval
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	Pending approval	Pending approval
Feb 07	MAOI Antidepressants	▪ transdermal selegiline (Emsam)	ECF	▪ phenelzine (Nardil)	Pending approval	Pending approval
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	24 Jan 07 (to coincide with May 06 meeting decision)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide / Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	21 Feb 07 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. February 2007 DoD P&T Committee Meeting

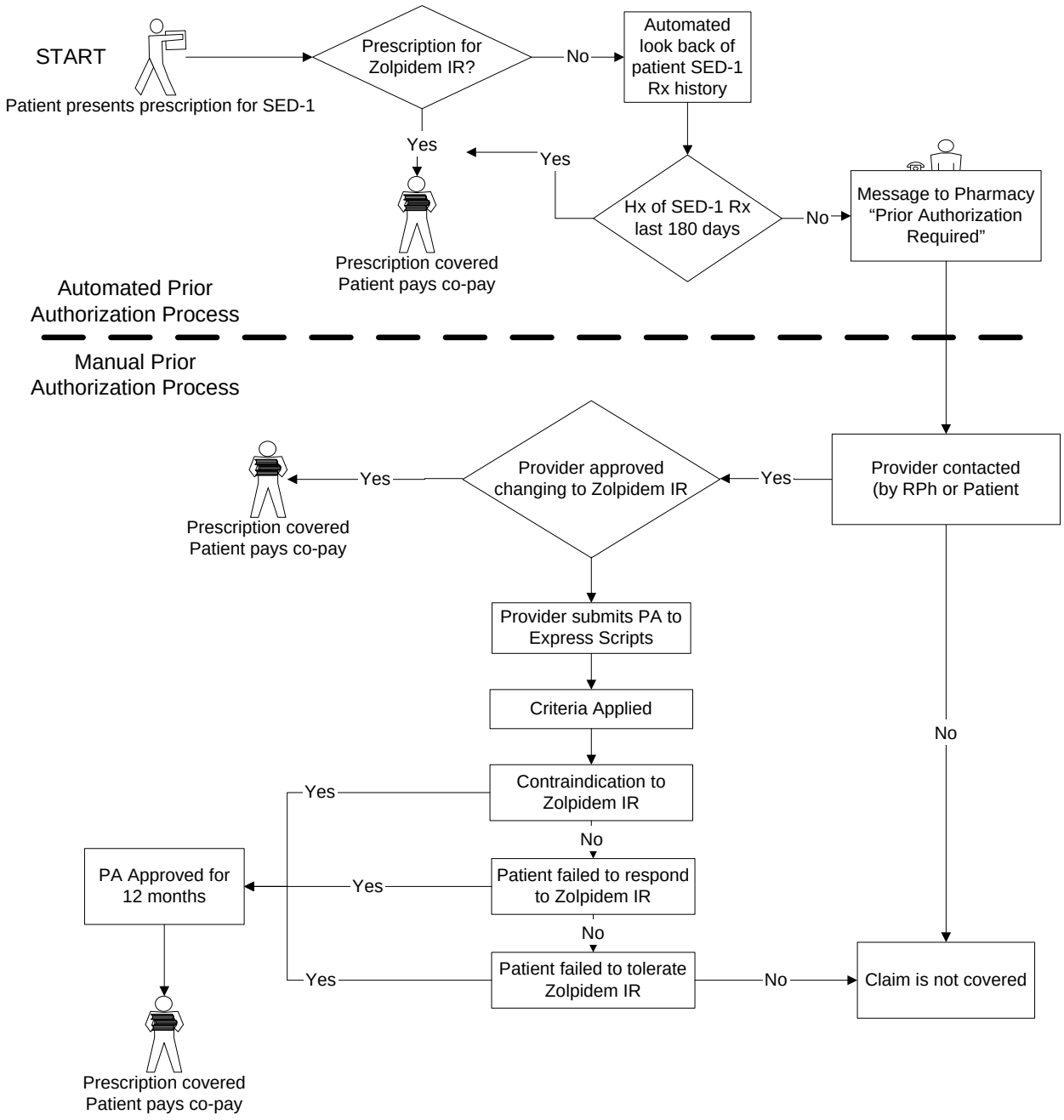
Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Sitagliptin phosphate tablets (Januvia ;Merck) Oral hypoglycemic drug (dipeptidyl peptidase IV [DPP4] inhibitor)	Oct 06 (launched Nov 06) ▪ For use as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus ▪ For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, or a thiazolidinediones when the single agent alone, with diet and exercise, does not provide adequate glycemic control. ▪ Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings	No UF recommendation at this meeting. Consideration of UF status deferred until oral hypoglycemic drugs are reviewed; UF review not anticipated for 12 months.
Paliperidone extended release tablets (Invega; Janssen/ALZA)) Atypical antipsychotic	Dec 06 (launched Jan 07) ▪ Treatment of schizophrenia ▪ Efficacy in acute treatment of schizophrenia established in three 6-week, placebo controlled, fixed-dose trials in subjects with schizophrenia. ▪ Efficacy not evaluated in placebo-controlled trials for longer than six weeks; physicians electing to use paliperidone for extended periods should periodically re-evaluate long-term usefulness	No UF recommendation at this meeting. Consideration of UF status deferred until atypical antipsychotics are reviewed; UF review not anticipated for 12 months.

Appendix C – Table 3. Table of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APAP	acetaminophen
ASA	aspirin
BAK	benzalkonium chloride
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
CNS	central nervous system
CYP	cytochrome P450
DEA	Drug Enforcement Agency
DERP	Drug Effectiveness Review Project
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
ESA	erythropoiesis stimulating agents
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
HAM-D	Hamilton Rating Scale for Depression
IOP	intraocular pressure
IR	immediate release
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MHS	Military Health System
MTF	military treatment facility
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPI	proton pump inhibitor
RCT	randomized controlled trial
SED-1s	newer sedative hypnotics
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary

Appendix D – Figure 1. Prior Authorization Process for SED-1 Agents Other than Zolpidem IR (Ambien)

Figure 1. TRICARE Pharmacy Network Step Therapy Process
Newer Sedative Hypnotics (SED-1)



DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2006

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF): The P&T Committee was briefed on four new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration. The committee discussed the need for quantity limits and prior authorization (PA) for two of the new drugs, human insulin inhalation powder (Exubera) and fentanyl buccal tablets (Fentora); there are existing quantity limits for other inhaled products and fentanyl lozenges. No recommendations were made for human insulin inhalation powder, as typical dosage requirements and utilization are unclear at this time. The Committee deferred a decision on quantity limits for fentanyl buccal tablets until the narcotic analgesic class is reviewed at an upcoming meeting.

Contraceptive Agents 30/10 mcg ethinyl estradiol (EE)/0.15 mg levonorgestrel for extended use, (Seasonique), and 20 mcg ethinyl estradiol (EE)/1 mg norethindrone acetate – 24 day regimen, (Loestrin 24 Fe).

Background: Two new contraceptive products, Seasonique and Loestrin 24 Fe, have been marketed since the contraceptive drug class was reviewed in May 2006.

Seasonique - Seasonique is a monophasic oral contraceptive with 30 mcg of EE specifically packaged and labeled for extended cycle use (84 days of 30 mcg EE/0.15 mg levonorgestrel, followed by seven days of low-dose estrogen [10 mcg EE]). The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial.

The difference between Seasonale, a non-formulary (third) tier agent, and Seasonique is the substitution of seven low-dose estrogen (10 mcg EE) tablets in Seasonique for the seven placebo tablets in Seasonale. For this reason, Seasonique's regimen cannot be exactly duplicated by using conventional packages of Nordette or its equivalents and discarding unneeded placebo tablets, unlike Seasonale. With respect to efficacy in preventing pregnancy, there is no reason to believe that Seasonique would differ from other similar oral contraceptives.

Loestrin 24 FE: Loestrin 24 Fe is a monophasic oral contraceptive product with 20 mcg EE packaged as a 24-day regimen (24 days of 20 mcg EE /1 mg norethindrone followed by four days of placebo tablets).

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive effectiveness with low estrogen products; however, there is no supporting clinical evidence. An alternative using conventionally packaged Loestrin Fe 1/20 that may accomplish the same general goal would be to simply start a new package early.

Relative Clinical Effectiveness Conclusion: The Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other oral contraceptives included on the UF.

Relative Cost Effectiveness Conclusion: Cost minimization analysis (CMA) showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg EE and Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg EE. Based on the results of the CMAs and other clinical and cost considerations, the Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe are substantially more costly than other oral contraceptives containing 30 mcg EE or 20 mcg EE included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Seasonique and Loestrin 24 Fe, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF. (See paragraphs 5B1, 5B2 and 5B3 on pages 14-16 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Seasonique and Loestrin 24 Fe and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for the contraceptive agents. (See paragraph 5B4 on page 17 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5B5 on page 17 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement January 24, 2007"*

Topical antifungal agents – 0.25% miconazole, 15% zinc oxide, 81.35% white petrolatum ointment (Vusion)

Background: The topical antifungal agents were reviewed by the Committee in Aug 2005. A new ointment containing 0.25% miconazole, 15% zinc oxide, and 81.35% white petrolatum (Vusion) has been approved by the FDA. Vusion contains a much lower concentration of miconazole than other prescription and OTC miconazole products (0.25% vs. 2%) and is only available in an ointment formulation.

Vusion is specifically labeled for the adjunctive treatment of diaper dermatitis only when complicated by microscopically-documented candidiasis in immunocompetent pediatric patients four weeks and older.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that although Vusion is labeled for a specific type of diaper dermatitis in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other topical antifungals included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that Vusion is the least cost-effective of all comparators, including other antifungals commonly used for diaper rash, when analyzed on a cost per utilizer basis. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that Vusion is substantially more costly than other antifungals commonly used for the treatment of the same condition.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determination for Vusion, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Vusion be classified as non-formulary under the UF. (See paragraphs 5C1, 5C2 and 5C3 on pages 17-19 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Vusion and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for Vusion. (See paragraph 5C4 on page 19 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5C5 on page 19 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement in 30 days."*

Antiemetic Agents - Nabilone (Cesamet)

Background: The Committee previously reviewed the antiemetic agents in May 2006. Nabilone is a synthetic cannabinoid antiemetic similar to dronabinol. Nabilone is indicated for treatment of chemotherapy-induced nausea and vomiting when conventional antiemetics have failed. There are no published clinical trials comparing nabilone with dronabinol, or with the 5-hydroxytryptamine-3 (5-HT3) antagonists.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that while nabilone offers a slight convenience of dosing frequency compared to dronabinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other antiemetics included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that nabilone has a cost-effectiveness profile that is similar to dronabinol. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that nabilone is comparable in cost to dronabinol, a similar cannabinoid antiemetic included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for nabilone, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that nabilone be classified as formulary on the UF.

(See paragraphs 5D1, 5D2 and 5D3 on pages 20-21 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – OLDER SEDATIVE HYPNOTICS (SED-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Older Sedative/Hypnotic (SED-2) Medications. The SED-2 drug class is comprised of five hypnotic benzodiazepines: estazolam, flurazepam, quazepam, temazepam, and triazolam; two barbiturate hypnotics: butabarbital and secobarbital; and one nonbarbiturate hypnotic agent: chloral hydrate. All eight of these drugs have been marketed for a number of years, and all but quazepam, butabarbital, and two less commonly used strengths of temazepam are available in generic formulations. The SED-2 drug class accounted for $2.5 million in Military Health System (MHS) expenditures for the period Aug 2005 to July 2006 and is ranked #165 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion: The Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The five hypnotic benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) are widely considered interchangeable for the treatment of short-term insomnia when used in equipotent doses, despite differences in onset and duration of action.
2) Temazepam is the most desirable benzodiazepine in the SED-2 drug class, based on clinical factors (duration of action, tolerance to therapeutic effects, adverse effect profile).
3) The hypnotic barbiturates, secobarbital and butabarbital, have fallen out of favor compared to newer therapies, primarily due to safety concerns, and are infrequently utilized at any MHS point of service.
4) Chloral hydrate appears to have a unique niche in the setting of outpatient pediatric sedation.
5) There are no clinical reasons to justify designating any of the SED-2s as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Secobarbital, chloral hydrate, flurazepam, temazepam 15 and 30 mg, estazolam, and triazolam have similar relative cost-effectiveness.
2) Butabarbital, quazepam, and temazepam 7.5 and 22.5mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost

effectiveness determinations for the SED-2s, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that estazolam, flurazepam, quazepam, temazepam, triazolam, butabarbital, secobarbital, and chloral hydrate be maintained as formulary on the UF, and that none of the SED-2s be classified as non-formulary under the UF. (See paragraphs 6A, 6B and 6C on pages 22-24 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining the generically available strengths of temazepam (15 mg and 30 mg) as the BCF selections in this class, excluding the 7.5 mg and 22.5 mg proprietary dosage strengths. (See paragraph 6F on page 25 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

The drugs in the Attention-Deficit / Hyperactivity Disorder (ADHD) and Narcolepsy Agents class are comprised of the following: for ADHD, there is one non-stimulant: atomoxetine (Strattera) and five stimulant compounds: methylphenidate, mixed amphetamine salts, dexmethylphenidate, dextroamphetamine, and methamphetamine; for narcolepsy, there are two drugs: modafinil (Provigil) and sodium oxybate (Xyrem). The ADHD and Narcolepsy Agents accounted for approximately $84.5 million dollars in MHS expenditures for Fiscal Year (FY) 2006 and are ranked #16 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following:

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.

2) There is no evidence to suggest a difference in efficacy between immediate release (IR) formulations of methylphenidate, dextroamphetamine, dexmethylphenidate, and mixed amphetamine salts.

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the

products. Methylphenidate 30% IR/70% extended release (ER) (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.

4) Mixed amphetamine salts extended release (ER) (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.

5) The efficacy of atomoxetine appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The methylphenidate transdermal system can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Atomoxetine remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) Responders to a provider survey expressed a desire for availability of the following products to cover clinical needs: methylphenidate OROS, an IR methylphenidate product, mixed amphetamine salts ER, and atomoxetine.

12) The narcolepsy drug modafinil provides a unique niche in therapy as a wakefulness promoting agent.

13) The narcolepsy drug sodium oxybate has a high incidence of adverse events, but serves a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the cost analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Once daily ADHD agents: dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) Multiple daily use ADHD agents: dexmethylphenidate IR (Focalin) was not cost-effective relative to the other agents in the subclass.

3) Agents indicated in the treatment of narcolepsy: Although modafinil (Provigil) and sodium oxybate (Xyrem) were more costly relative to other agents indicated for the

treatment of narcolepsy, they possessed unique clinical advantages relative to other agents within the class.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate sustained-release (SR) (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the UF and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) be classified as non-formulary under the UF. (See paragraphs 7A, 7B and 7C on pages 25-39 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA **-** Based on the clinical evaluation for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), and dexmethylphenidate SODAS (Focalin XR), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin) and dexmethylphenidate SODAS (Focalin XR). (See paragraph 7D on page 39-40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD **-** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 7E on page 40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION - The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin, generics) as the BCF selections in this class. (See paragraph 7F on page 40 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. PRIOR AUTHORIZATION REQUIREMENT (PA) FOR MODAFINIL (PROVIGIL)

The P&T Committee agreed that a PA was needed for modafinil, due to the potential for inappropriate use.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following approval by the Director, TMA. The Committee voted (15 for, 0 against, 0 abstained, 2 absent) to recommend PA criteria. (See paragraph 8 on pages 40-42 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. PA REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS)

COMMITTEE ACTION – Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The criteria recommended by the P&T Committee are based on safety requirements in labeling and incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 41-43 of the P&T Committee minutes for rationale and summary of PA criteria.) The P&T Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. (See paragraph 9 on pages 42-43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Table 1. Implementation Status of UF Recommendations/Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

William Winkenwerder, Jr., M.D.
Date: 17 January 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
15 November 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14 November 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
MAJ Travis Watson, MSC, USA *for* CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
No replacement *for* LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Charlene Reith *for* LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Walter Downs, MC *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
CDR David Tanen, MC	Navy, Physician at Large
LT Tim Thompson *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC for COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

COL Isiah Harper, MSC	Army, Pharmacy Officer
LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer (Pharmacy Consultant)
CAPT David Price, MSC	Navy, Pharmacy Officer (Pharmacy Consultant)

C. Non-Voting Members Present

Mr. Lynn T. Burleson	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR

D. Non-Voting Members Absent

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

E. Others Present

Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms. Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms. Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms. Julie Liss	DoD Pharmacoeconomic Center
Ms. Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms. Harsha Mistry	DoD Pharmacoeconomic Center
Col Nancy Misel	IMA DoD PEC
Janet Dailey	VAPBM
Charles R. Brown	TMA/CMB

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – August 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted, however, there was a correction to the decision paper. The sentence on page 3, section B (Committee Action: Basic Core Formulary (BCF) Recommendation), line 3 was revised to "The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF."

B. Approval of August Minutes - Dr. William Winkenwerder, Jr., M.D., approved the minutes of the August 2006 DoD P&T Committee meeting on 23 October 2006.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the P&T Committee regarding the August 2006 BAP meeting. The Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since August 2005. The Committee made the following observations:

1) **DuetAct (pioglitazone plus glimepiride) –** A new thiazolidinedione (TZD) combination agent has been marketed since the TZD class was reviewed in August 06. DuetAct is the combination of pioglitazone plus glimepiride. It is available in two strengths: 30mg pioglitazone/2mg glimepiride and 30mg pioglitazone/4mg glimepiride. The PEC informed the Committee that DuetAct was added to the UF as a line extension of the existing UF blanket purchase agreements (BPAs) and voluntary agreements for TRICARE retail pharmacy rebates (VARR) with the manufacturer.

2) **Implementation Status of UF Decisions –** The PEC briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since February 2005. The Committee made the following observations:

a) Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.

b) Collective utilization of UF agents across all reviewed drug classes and points of service (military treatment facility (MTF), TRICARE Mail Order Pharmacy Program (TMOP), and TRICARE Retail Network Pharmacy (TRRx)) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been an overall 30% reduction in the use of non-formulary agents (MTFs -89%, Mail +6%, Retail -11%), including those classes where implementation has only just begun. In classes with at least 6 months of implementation, there has been an overall 40% reduction in the use of non-formulary agents (MTFs -93%, Mail +1%, Retail -21%).

c) The cost per day of treatment across all reviewed drug classes has decreased, but magnitude varies by point of service. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been an overall 5% reduction in the cost per day of treatment (MTFs -23%, Mail -5%, Retail -2%), including those classes where implementation has only just begun. In classes with at least 6 months of implementation, there has been an overall 7% reduction in the cost per day of treatment (MTFs -30%, Mail -5%, Retail -4%).

d) Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and point of service.

e) Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares for UF agents than the unmanaged points of service (i.e., TMOP and TRRx).

f) It appears that more beneficiaries may be electing to receive non-formulary medications through TMOP.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on four new drugs that were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed.

The P&T Committee discussed the need for quantity limits or prior authorization (PA) requirements for two of these products: inhaled insulin (Exubera) and fentanyl buccal tablets (Fentora). Quantity limits are in place for other inhaled products (e.g., for asthma) and for fentanyl transmucosal lozenges or "lollipops" (Actiq). Some other health plans require PA for human insulin inhalation powder. The Committee agreed that more information was needed before making recommendations; the Narcotic Analgesic drug class is scheduled for UF review in February 2007.

B. Contraceptive Agents - 30/10 mcg ethinyl estradiol (EE)/0.15 mg levonorgestrel for extended use, (Seasonique), and 20 mcg ethinyl estradiol (EE)/1 mg norethindrone – 24 day regimen, (Loestrin 24 Fe)

1) *Relative Clinical Effectiveness* – Two new contraceptive products, Seasonique and Loestrin 24 Fe, have been marketed since the contraceptive drug class was reviewed in May 06.

Seasonique – Seasonique is a monophasic oral contraceptive with 30 mcg of EE specifically packaged and labeled for extended cycle use (84 days of 30 mcg EE/0.15 mg levonorgestrel, followed by seven days of low-dose estrogen [10 mcg EE]).

The UF contains multiple monophasic oral contraceptives containing 30 mcg of EE in combination with various progestogens. These products include Yasmin (3 mg

drospirenone) and generic equivalents to Desogen (0.15 mg desogestrel); Loestrin 1.5/30, Loestrin Fe 1.5/30 (1.5 mg norethindrone); Lo/Ovral (0.3 mg norgestrel); and Nordette (0.15 mg levonorgestrel). Two of these (Nordette equivalent products and Yasmin) are on the BCF. All of these products are available in conventional 28-day packaging (21 days of active tablets followed by 7 days of placebo tablets).

Another extended cycle product, Seasonale, was placed in the third (non-formulary) tier of the UF following the May 06 meeting, with an effective date of 24 Jan 2007. The difference between Seasonale and Seasonique is the substitution of the seven low-dose estrogen (10 mcg EE) tablets in Seasonique for the seven placebo tablets in Seasonale. For this reason, Seasonique's regimen cannot be exactly duplicated by using conventional packages of Nordette or its equivalents and discarding unneeded placebo tablets, unlike Seasonale.

The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial. One other oral contraceptive product offering low-dose estrogen during the off period is available (Mircette, Kariva, and equivalents; 21 days of 20 mcg EE/0.15 mg desogestrel followed by 2 days of placebo and 5 days of 10 mcg EE). It is worth noting that utilization of this product, which is included on the UF, is relatively low compared to other 20 mcg EE products. Alternatives to Seasonique in women being treated on an extended cycle basis who are experiencing menstrual-related problems during the four annual off periods include addition of a low-dose conjugated estrogen product (e.g., 0.3 mg Premarin) during the off period, or decreasing the length or number of off periods.

With respect to efficacy in preventing pregnancy, there is no reason to believe that Seasonique would differ from other similar oral contraceptives. One non-controlled trial evaluating Seasonique in 1,000 women reported that it was >99% effective in preventing pregnancy; there are no head-to-head trials comparing Seasonique with other contraceptives.

Loestrin 24 Fe – Loestrin 24 Fe is a monophasic oral contraceptive product with 20 mcg EE packaged as a 24-day regimen (24 days of 20 mcg EE / 1 mg norethindrone followed by four days of placebo tablets).

The UF contains multiple monophasic oral contraceptives containing 20 mcg of EE in combination with various progestogens, including Yaz (3 mg drospirenone) and equivalents to Alesse (0.1 mg levonorgestrel) and Loestrin 1/20 / Loestrin Fe 1/20 (1.0 mg norethindrone). Alesse equivalent products and Yaz are on the BCF. Like Loestrin 24 Fe, Yaz is a 24-day regimen product; Alesse, Loestrin 1/20, and Loestrin Fe 1/20 are available in conventional 28-day packaging (21 days of active tablets followed by 7 days of placebo tablets). Loestrin 24 Fe offers the same daily estrogen and progestogen content as the existing Loestrin Fe 1/20 product (and its generic equivalents), differing only in the number of active and placebo tablets included.

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive

effectiveness with low estrogen products; however, there is no supporting clinical evidence. One trial in 938 women compared Loestrin 24 Fe with Loestrin Fe 1/20 and reported a Pearl Index (number of pregnancies per 100 women per year of use) of 1.85 (five pregnancies) with the 24-day regimen vs. 1.79 (two pregnancies) with the 21-day regimen (no statistics provided). There were no differences between the two products in terms of serious adverse events, treatment-related adverse events, and discontinuations due to adverse events.

An alternative using conventionally packaged Loestrin Fe 1/20 that may accomplish the same general goals as with the 24-day regimen would be to simply start a new package early.

Conclusion: The Committee concluded that Seasonique or Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over other oral contraceptives included on the UF.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost-effectiveness of Seasonique and Loestrin 24 Fe in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the contraceptive drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Seasonique or Loestrin 24 Fe differed with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the contraceptive class. As a result, two cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of Seasonique and Loestrin 24 Fe.

   The CMA for Seasonique compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 30 mcg of EE, as listed above. The CMA for Loestrin 24 Fe compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 20 mcg of EE, as listed above.

   Conclusion for Seasonique: The results of the CMA showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg EE.

   Conclusion for Loestrin 24 Fe: The results of the CMA showed that Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg EE.

3) *UF Recommendations* – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF.

4) *Medical Necessity Criteria* – Based on the clinical evaluation of Seasonique, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for Seasonique:

   a) Use of formulary alternatives is contraindicated.

   b) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

   c) Use of formulary alternatives has resulted in therapeutic failure.

   Based on the clinical evaluation of Loestrin 24 Fe, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for Loestrin 24 Fe:

   a) Use of formulary alternatives is contraindicated.

   The P&T Committee did not agree that other general medical necessity criteria would apply to Loestrin 24 Fe given the UF status of Loestrin Fe 1/20, which contains the same combination of the same active ingredients and which can be used on the same shortened off-period basis by discarding unneeded placebo tablets.

   COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

5) *UF Implementation Period* – The P&T Committee discussed the advantages and disadvantages of a longer versus a shorter implementation period for Seasonique and Loestrin 24 Fe. The fact that Seasonique is packaged as a three-month supply supported a longer implementation period, while a shorter implementation period would avoid patient disruption as utilization of new products increases. As of Oct 2006, there have been 161 unique utilizers of Seasonique and 2,227 of Loestrin 24 Fe, at all three points of service. The P&T Committee also discussed the prospect for coordinating implementation of non-formulary status for Seasonique and Loestrin 24 Fe with the already established effective date for Seasonale non-formulary status (24 Jan 07), but it was unclear if this was possible given timelines for the BAP meeting and subsequent review of P&T minutes and BAP comments by the Director, TMA. Ultimately, the Committee recommended a shorter implementation period because it would avoid patient disruption as utilization of new products increases.

   COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

C. Topical Antifungal Agents - 0.25% miconazole, 15% zinc oxide, 81.35% white petrolatum ointment (Vusion)

1) *Relative Clinical Effectiveness:* The topical antifungal agents were reviewed by the P&T Committee in Aug 05. Topical antifungal agents included on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat, generics), ketoconazole (Nizoral, generics), butenafine (Mentax, generics),

and naftifine (Naftin). Clotrimazole (Lotrimin, generics) and nystatin (Mycostatin, generics) are classified as BCF agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics), and oxiconazole (Oxistat).

Vusion contains 0.25% miconazole along with 15% zinc oxide and 81.35% white petrolatum, and is only available as an ointment. Over-the-counter (OTC) and prescription miconazole products contain a 2% concentration of miconazole, and are available in several formulations (e.g., cream, ointment, spray, spray liquid, powder, and solution). The zinc oxide and petrolatum components of Vusion are skin protectants; numerous OTC products (e.g., Balmex, Happy Hiney) contain varying amounts of these two ingredients, which form a physical barrier on the skin.

Vusion is specifically labeled for the adjunctive treatment of diaper dermatitis only when complicated by microscopically-documented candidiasis in immunocompetent pediatric patients four weeks and older. Vusion is the first product with a labeled indication for diaper rash in infants as young as four weeks, and the first one to include candidiasis in the label. Vusion is not approved for use in adults, immunocompromised patients, or infants with diaper rash that is not confirmed to have candidiasis as the causative factor. The Committee agreed that Vusion is likely to be used for non FDA-approved indications, particularly for diaper rash without documented candidiasis. The existing BCF and UF topical antifungal products have much broader indications than Vusion and treat several types of infections (e.g., tinea pedis, tinea corporis, tinea cruris, or tinea capitis).

The rationale for Vusion incorporating a low concentration of 0.25% miconazole is to provide efficacy and safety in young infants without achieving measurable plasma concentrations. It is not clear, however, that Vusion is the only topical antifungal that may be used for this purpose. Nystatin (Mycostatin, generics) can be used in infants as young as neonates, and the package insert states that it is well tolerated, even in debilitated infants, even with prolonged administration. Both miconazole (Monistat, generics) 2% and clotrimazole (Lotrimin, generics) 1% can be used in children as young as two years of age.

There are no published clinical trials comparing Vusion with other miconazole formulations, clotrimazole (Lotrimin, generics) or nystatin (Mycostatin, generics). One published, 330-patient trial compared Vusion with a zinc oxide/petrolatum vehicle and reported a complete cure rate after seven days of 7% with Vusion versus 0.8% with vehicle; adverse event rates with Vusion were similar to vehicle.

Conclusion: The P&T Committee concluded that, although Vusion is labeled for a specific type of diaper dermatitis in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over other topical antifungals included on the UF.

2) *Relative Cost Effectiveness:* The P&T Committee evaluated the relative cost-effectiveness of Vusion in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the topical antifungal drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Vusion differed significantly with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the topical antifungal class. As a result, a CMA was performed to determine the relative cost-effectiveness of Vusion within the topical antifungal drug class.

The CMA for Vusion compared the weighted cost per treated utilizer across all three points of service to other antifungal agents previously analyzed during the DoD P&T Committee's August 2005 review of topical antifungals. Comparative antifungals used specifically for diaper rash included clotrimazole (Lotrimin, generics), miconazole (Monistat, generics), and nystatin (Mycostatin, generics). Other topical antifungals compared included cyclopirox (Loprox, generics), sertaconazole (Ertaczo), oxiconazole (Oxistat), naftifine (Naftin), butenafine (Mentax), sulconazole (Exelderm), econazole (Spectazole, generics), and ketoconazole (Nizoral, generics).

Conclusion: The results of the CMA showed that Vusion is the least cost-effective of all comparators, when analyzed on a cost per utilizer basis.

3) *UF Recommendation:* The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Vusion be classified as non-formulary under the UF.

4) *Medical Necessity Criteria:* Based on the clinical evaluation of Vusion, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for Vusion:

   a) Use of formulary agents is contraindicated.

   b) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

   COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

5) *UF Implementation Period:* The P&T Committee recommended an implementation period of 60 days, due to existing low utilization in the MHS. As of October 2006, a total of 581 Vusion prescriptions have been dispensed at all three points of service. For the six month period between Apr 2006 and Oct 2006, there have been 426 unique utilizers of Vusion in the MHS.

   COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

D. Antiemetic Agents (Cesamet)

1) *Relative Clinical Effectiveness:* The Committee previously reviewed the antiemetic agents at the May 06 P&T meeting. The antiemetic class includes the following agents, which may be sub-classified based on typical use and mechanism of action. All of these agents are on the UF with the exception of dolasetron (Anzemet).

   - *The newer antiemetics*
     - 5-hydroxytryptamine-3 [5-HT3] antagonists: ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet)
     - Neurokinin-1 (NK-1) antagonist: aprepitant (Emend)
   - *The older antiemetics*
     - Cannabinoids: dronabinol (Marinol)
     - Antihistamines: meclizine (Antivert, generics) and promethazine (Phenergan, generics). Promethazine is on the BCF.
     - Phenothiazines: prochlorperazine (Compazine, generics), thiethylperazine (Torecan)
     - Anticholinergics: trimethobenzamide (Tigan, generics), transdermal scopolamine (Transderm Scop)

   Nabilone (Cesamet) is a synthetic cannabinoid antiemetic similar to dronabinol. It was previously approved for marketing in 1985, but withdrawn by the manufacturer in 1989 due to commercial reasons not related to efficacy or safety. It is indicated for treatment of chemotherapy-induced nausea and vomiting (CINV) when conventional antiemetics have failed. The other available cannabinoid antiemetic, dronabinol, is also indicated for CINV, but has an additional indication for treating anorexia in patients with AIDS. The duration of action of nabilone is longer than dronabinol: 8-12 hours vs. 4-6 hours. This allows for a dosing regimen of BID-TID (2 to 3 times a day) with nabilone, compared to TID-QID (3 to 4 times a day) for dronabinol.

   There are no published clinical trials comparing nabilone with dronabinol (Marinol). Additionally, there are no trials comparing nabilone with any of the 5-HT3 antagonists—ondansetron, granisetron, or dolasetron – which have replaced older antiemetics as the standard of care for CINV. Nabilone was approved by the FDA based on clinical trial data submitted in the early 1980s. In published trials, nabilone showed superior efficacy to prochlorperazine, but with an increased incidence of adverse effects; another trial found the combination of nabilone plus prochlorperazine inferior to a combination of dexamethasone plus metoclopramide.

   The psychoactive adverse effects of nabilone relegate it to use as a second-line agent. Nabilone is a DEA (Drug Enforcement Administration) Schedule II drug, compared to dronabinol, a Schedule III drug.

   Conclusion: The P&T Committee concluded that, while nabilone offers a slight convenience of dosing frequency compared to the other cannabinoid antiemetics, dronabinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antiemetics included on the UF.

2) *Relative Cost Effectiveness:* The P&T Committee evaluated the relative cost-effectiveness of nabilone in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the antiemetic class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that nabilone differed with regards to efficacy, safety, tolerability, or clinical outcomes compared to the other antiemetics. As a result, a CMA was performed to determine the relative cost-effectiveness of the nabilone within the antiemetic drug class.

   The CMA compared the ranges of cost per day of treatment at all three points of service (at recommended starting doses) for nabilone versus the other cannabinoid antiemetic dronabinol, which is currently included on the UF.

   Conclusion: The results of the CMA showed that nabilone has a cost-effectiveness profile that is similar to dronabinol.

3) *UF Recommendations:* The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that nabilone be maintained as formulary on the UF.

4) *Medical Necessity Criteria:* Since nabilone was not recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

5) *UF Implementation Period:* Since nabilone was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – OLDER SEDATIVE HYPNOTICS (SED-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Older Sedative/Hypnotic Medications (SED-2s). The SED-2 drug class is comprised of five hypnotic benzodiazepines: estazolam (Prosom, generics), flurazepam (Dalmane, generics), quazepam (Doral), temazepam (Restoril, generics), and triazolam (Halcion, generics); two barbiturate hypnotics: butabarbital (Butisol) and secobarbital (Seconal, generics); and one nonbarbiturate hypnotic agent: chloral hydrate (generics). All eight of these drugs have been marketed for a number of years, and all but quazepam (Doral), and the 7.5 mg and 22.5 mg strengths of temazepam (Restoril) are available in generic formulations. The SED-2 drug class accounted for $2.5 million in MHS expenditures for the period August 2005 to July 2006 and is ranked #165 in terms of total expenditures during that time period. In terms of numbers of prescriptions dispensed for all sedative hypnotics in the MHS, the SED-2 agents account for 20% of the overall market, with the newer non-benzodiazepine sedative

hypnotics – eszopiclone (Lunesta), zolpidem (Ambien), ramelteon (Rozerem) and zaleplon (Sonata) – accounting for the remaining 80%.

A. SED-2s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the SED-2s currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) Efficacy

Hypnotic benzodiazepines – The hypnotic benzodiazepines [estazolam (Prosom, generics), flurazepam (Dalmane, generics), quazepam (Doral), temazepam (Restoril, generics), and triazolam (Halcion, generics)] are indicated for the short-term (two weeks or less) treatment of insomnia. When given before bedtime, all five hypnotic benzodiazepines have been shown in numerous clinical trials to improve total sleep time, sleep latency, and number of awakenings, and they are effective in reducing early morning awakening. When used in equipotent doses, all the hypnotic benzodiazepines are effective and considered therapeutically interchangeable for short-term treatment of insomnia. Like other benzodiazepines, the hypnotic benzodiazepines are also effective in treating anxiety disorders.

Temazepam (Restoril, generics) is frequently preferred over flurazepam (Dalmane, generics), as the latter has a long half-life (47-160 hours compared to 3.5-18.4 hours for temazepam) that increases the occurrence of residual sedative effects. Triazolam (Halcion, generics) is commonly considered by providers to have an unacceptable adverse effect profile. Quazepam (Doral) and estazolam (Prosom, generics) are infrequently used; they were late entrants to the market, have longer half-lives, and offer no real clinical advantage compared to temazepam.

The agents are selected for clinical use according to their pharmacokinetic profiles (onset of action, duration of action), which vary among the agents. Although much of their usage has been supplanted by the newer sedative hypnotic drug class, the hypnotic benzodiazepines are still utilized for the short-term treatment of insomnia.

Hypnotic barbiturates – The hypnotic barbiturates include butabarbital (Butisol), and secobarbital (Seconal, generics). Secobarbital has been used in the short-term treatment of insomnia, and also in the pre-operative setting and in alcohol withdrawal. Butabarbital (Butisol) has a half-life of 34 to 42 hours, and is also effective as a sedative.

The hypnotic barbiturates have no safety or efficacy advantage compared to the benzodiazepines or newer sedative hypnotics, and their use has largely fallen out of favor for the treatment of insomnia. They may have a niche in therapy when the

benzodiazepines or newer hypnotics are contraindicated in an individual patient, or in the setting of pre-operative sedation.

Chloral hydrate - Chloral hydrate is no longer routinely used as a primary treatment for insomnia, as it is not as effective as the benzodiazepines. Chloral hydrate is more commonly used preoperatively or prior to procedures to ally anxiety or induce sedation. It has a unique niche for use in the setting of outpatient pediatric sedation, due to the perception that chloral hydrate produces less paradoxical excitement than the barbiturates. Chloral hydrate is included in the 1992 update to the American Academy of Pediatric (AAP) guidelines for pediatric sedation.

2) Safety / Tolerability

Benzodiazepines – There are no major differences between the five hypnotic benzodiazepines with respect to safety and tolerability. Adverse events that include daytime sedation, memory problems, and falls may limit utility, especially in the elderly. There are also concerns that benzodiazepines may limit deep sleep. The class is deemed relatively safe based on more than 30 years of clinical use. The agents have differing safety profiles with respect to drug interactions, anterograde amnesia, and daytime sedation. All benzodiazepines are contraindicated in pregnancy.

Hypnotic barbiturates – The hypnotic barbiturates have multiple safety and abuse/addiction concerns and a self-limiting mechanism of action; overdoses can be lethal. They also induce the action of hepatic microsomal drug-metabolizing enzymes, leading to increased metabolism of many drugs and endogenous substrates, such as steroid hormones, cholesterol, bile salts, and several others. Secobarbital (Seconal, generics) and butabarbital (Butisol) have been associated with withdrawal symptoms, such as multiple seizures or psychosis similar to alcohol delirium; disorientation, hallucinations, and even death have been reported. They are classified as pregnancy category D. These products were largely replaced by the benzodiazepines.

Chloral hydrate – Chloral hydrate has been associated with cardiac dysrhythmias in both adults and children. Chloral hydrate has numerous safety concerns when it is administered to children for pre-operative sedation prior to the child's arrival at the clinic; however, when properly administered it is both safe and effective. The drug has not been studied in pregnancy; a limited number of reports indicate use with no fetal harm. The AAP recommends that, while chloral hydrate can be safely administered to lactating women, infants should be observed for symptoms of drowsiness as drug and metabolites are excreted into breast milk.

Clinical Effectiveness Conclusion – The older sedative hypnotic drugs still play a role in the treatment of insomnia and pre-operative sedation, although they have been largely replaced by newer agents in clinical practice. It is widely accepted that the five hypnotic benzodiazepines are therapeutically interchangeable, although temazepam (Restoril, generics) has the most favorable half-life and safety profile. The barbiturates and chloral hydrate are used infrequently and primarily for special patient populations. There are no clinical reasons to justify designating any of these eight drugs as non-formulary under the UF.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. SED-2s – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the SED-2 (older sedative hypnotic) agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

A cost-minimization analysis was employed to assess the relative cost-effectiveness of the agents within the SED-2 therapeutic class. The agents were evaluated on their weighted average cost per day of therapy. The results of the analysis showed all of the agents to have similar relative cost-effectiveness, with the exception of the brand-only agents: quazepam (Doral), butabarbital (Butisol), and temazepam (Restoril) 7.5 and 22.5mg. Although these agents were less cost-effective relative to the other agents in the class, the Committee agreed that little savings would be achieved by placing any of these agents in the non-formulary tier due primarily to their low current and projected MHS utilization/expenditures. Butabarbital and quazepam account for less than 0.25% of SED-2 prescriptions across the MHS and approximately 2% of annual SED-2 MHS expenditures. Temazepam (Restoril) 7.5 and 22.5 mg account for less than 5% of all MHS prescriptions for temazepam.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

3) Secobarbital (Seconal, generics), chloral hydrate (generics), temazepam (Restoril, generics) 15 and 30 mg, estazolam (Prosom, generics), and triazolam (Halcion, generics) have similar relative cost-effectiveness.

4) Butabarbital (Butisol), quazepam (Doral), and temazepam (Restoril) 7.5 and 22.5mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

C. SED-2s – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-2 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that butabarbital (Butisol), secobarbital (Seconal, generics), chloral hydrate (generics), quazepam (Doral), temazepam (Restoril), estazolam (Prosom, generics), and triazolam (Halcion, generics) be maintained as formulary on the UF and that no agents be classified as non-formulary under the UF.

D. SED-2s – Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

E. SED-2s – UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

F. SED-2s – Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that at least one SED-2 agent should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that temazepam (Restoril, generics) 15 and 30 mg be added to the BCF. These strengths of temazepam are generically available and represent more than 95% of temazepam prescriptions. Temazepam is the most commonly used, clinically preferred, and cost-effective SED-2 agent at all points of service.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend adding temazepam 15 and 30 mg as the BCF selection in this class.

7. DRUG CLASS REVIEW – ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

The drugs in the Attention-Deficit / Hyperactivity Disorder (ADHD) and Narcolepsy Agents class are comprised of the following: for ADHD, there is one non-stimulant: atomoxetine (Strattera) and five stimulant compounds: methylphenidate, mixed amphetamine salts, dexmethylphenidate, dextroamphetamine, and methamphetamine; for narcolepsy, there are two drugs: modafinil (Provigil) and sodium oxybate (Xyrem). The ADHD and Narcolepsy Agents accounted for approximately $84.5 million dollars in MHS expenditures for Fiscal Year (FY) 2006 and are ranked #16 in terms of total expenditures during that time period.

The ADHD stimulant drugs are further divided into once daily products and multiple daily use products, based on differences in drug delivery mechanism. There are four once daily methylphenidate formulations: 1) an osmotically controlled-release delivery system [OROS)] tablet (Concerta); 2) a 30% immediate release (IR) and 70% extended release (ER) beads in a capsule (Metadate CD); 3) a mixture of 50% IR and 50% ER beads in a capsule using a spheroidal oral drug absorption system [SODAS] (Ritalin LA); and 4) a transdermal system (Daytrana patch). The other stimulant once daily products include mixed amphetamine salts ER (Adderall XR) and dexmethylphenidate SODAS (Focalin XR).

Multiple daily use products include five methylphenidate products: Ritalin, Ritalin sustained release (SR) (generics), Metadate ER (generics), Methylin ER (generics), and Methylin (generics). Other multiple daily use products include mixed amphetamine salts IR (Adderall, generics), dexmethylphenidate IR (Focalin), dextroamphetamine IR (Dexedrine, Dextrostat, generics), and methamphetamine IR (Desoxyn, generics).

A. ADHD and Narcolepsy Agents – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ADHD and narcolepsy agents currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a

pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) Efficacy

a) ADHD Drugs

i) Standard Therapy – Stimulants have remained the mainstay of therapy for treating children with ADHD. A systematic review completed by the state of Oregon Health and Science University Drug Effectiveness Review Program (DERP) concluded that the overall response rate with the stimulants ranges from 60-80%, but varying definitions of response were reported in the clinical trials.

ii) Clinical Trials – Interpretation of the efficacy literature is difficult due to the poor study design of published trials, use of different outcome rating scales, the limited number of comparator trials available, small number of patients enrolled in the studies, and overall short duration of evaluation. Direct comparisons of the trials are difficult, due to wide heterogeneity among trials and use of different ADHD rating scales.

IR versus IR stimulant products – The DERP systematic review compared the clinical efficacy of dextroamphetamine IR (Dexedrine, Dextrostat, generics) to methylphenidate IR (Ritalin, generics); reviewers concluded that none of the studies showed an efficacy difference between the two IR stimulants.

Two studies [Pelham 1999, Pliska 2000] that compared methylphenidate IR (Ritalin, generics) vs. mixed amphetamine salts IR (Adderall, generics) did not show a difference in efficacy. A study [Wigal 2004] comparing dexmethylphenidate IR (Focalin) with Adderall also found no difference in efficacy between the two drugs. The Committee concluded that the current body of evidence does not indicate a difference in the efficacy between methylphenidate IR, dextroamphetamine IR, dexmethylphenidate IR, and mixed amphetamine salts IR.

IR versus once daily stimulant products – The DERP systematic review identified only three studies comparing IR with once daily stimulants that were of sufficient study design quality to evaluate; all three trials compared methylphenidate IR (Ritalin, generics) with methylphenidate OROS (Concerta). One trial [Pelham 2001] enrolling 70 patients found no difference in the teacher rating scale, but reported a statistically significant difference in the parent rating scale that favored Concerta over methylphenidate IR. In a small study assessing driving skills in six adolescents [Cox 2004], there was no difference between the drugs at four to six hours after dosing. However, at 9 to 12 hours after administration, there was a statistically significant difference favoring Concerta. Another study enrolling 282 patients [Wolraich 2001] reported no difference in efficacy. The Oregon systematic review reported that in short-term studies, once daily

Concerta was preferred over methylphenidate IR products. However in trials with a longer duration of evaluation, there was no efficacy difference reported.

Once daily stimulants vs. once daily stimulants – When comparing the once daily products, the different drug release mechanisms influence the timing of effect. Methylphenidate OROS (Concerta) releases 22% of the drug dose immediately followed by release of 78% of the drug over 12 hours. Methylphenidate SODAS (Ritalin LA) releases 50% of the dose immediately and the remaining 50% over an 8- to 9-hour period. The methylphenidate formulation of 30% IR/70% ER beads (Metadate CD) releases 30% of the dose immediately, followed by the remaining 70% over an 8 to 9 hour period.

The drug delivery system appeared to have direct bearing on the results of two studies comparing sustained release products. A trial in 184 patients comparing methylphenidate 30% IR/70% ER (Metadate CD) with methylphenidate OROS (Concerta) [Swanson 2004] used a classroom rating scale as the outcome measure. Metadate CD was superior to Concerta in the morning, and there was no difference between the two drugs in the afternoon. However, in the evening, Concerta was superior to Metadate CD, reflecting the long duration of Concerta via the OROS system.

Methylphenidate OROS (Concerta) was compared to methylphenidate SODAS (Ritalin LA) in a randomized crossover trial enrolling 36 patients [Lopez 2003] using the classroom rating scale. At the four hour assessment time, Ritalin LA 20 mg was superior to 18 mg and 36 mg doses of Concerta. At the eight hour assessment, there was no difference between the Ritalin LA 20 mg and Concerta 36 mg. This study did not include a 12-hour assessment.

Once daily mixed amphetamine salts ER (Adderall XR) was compared to methylphenidate OROS (Concerta) and placebo in a driving assessment test conducted in 35 adolescents [Cox 2006*]*. Concerta compared more favorably to placebo than did mixed amphetamine salts ER (Adderall XR).

Dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana): There are no published trials comparing the efficacy of dexmethylphenidate SODAS (Focalin XR) or methylphenidate transdermal system (Daytrana) with other once daily stimulants; only placebo control trials are available for both products. The pharmacokinetic profiles of both drugs reflect a 12-hour duration of action.

Atomoxetine (Strattera): The DERP systematic review evaluated four studies comparing the non-stimulant atomoxetine (Strattera) and placebo, and reported that atomoxetine was superior to placebo. One trial reported superior efficacy with that atomoxetine compared to methylphenidate IR (Ritalin, generics) [Kratochvil 2002], while another other trial [Sangal 2004] reported no difference in efficacy. Three trials comparing atomoxetine with

either Concerta [Kremmer 2004; Michelson 2004] or Adderall XR [Wigal 2004] showed superior efficacy of the stimulants over atomoxetine.

iii) Treating non-responders – One study evaluating treatment response compared methylphenidate IR (Ritalin, generics) with dextroamphetamine IR (Dexedrine, Dextrostat, generics) [Efron 1997], and concluded that 40% to 80% of patients who did not respond to the initial stimulant would respond to the second stimulant. Clinically, patients who do not respond to a methylphenidate formulation often receive a trial of mixed amphetamine salts IR or ER (Adderall, Adderall XR).

iv) Clinical efficacy conclusion – All stimulant and non-stimulant formulations reviewed, no matter the delivery mechanism, have superior efficacy to placebo. Based on the limited data available, there does not appear to be a difference in efficacy between methylphenidate IR (Ritalin, generics), dextroamphetamine IR (Dexedrine, Dextrostat, generics), dexmethylphenidate IR (Focalin) and mixed amphetamine salts IR (Adderall, generics). Studies comparing IR to once daily methylphenidate products overall yielded no apparent difference in efficacy. The efficacy outcomes of studies comparing once daily methylphenidate products are dependent on the individual release mechanisms of the drugs. Methylphenidate 30% IR/70% ER (Metadate CD) and methylphenidate SODAS (Ritalin LA) showed superior efficacy to methylphenidate OROS (Concerta) at four and eight hour timeframes respectively. Concerta has an efficacy advantage over the other once daily products at the 9-12 hour timeframe. The only products with a sustained 12-hour effect are Concerta, dexmethylphenidate ER (Focalin XR), and methylphenidate transdermal system (Daytrana). The stimulants Concerta and mixed amphetamine salts ER (Adderall XR) appear to have superior efficacy compared to atomoxetine (Strattera).

b) Narcolepsy Drugs

i) Pharmacology

Modafinil (Provigil) – The exact mechanism of action by which modafinil promotes wakefulness is unknown. In contrast to drugs with high addiction potential (e.g., cocaine, amphetamine), modafinil only weakly stimulates receptors in the brain that play a role in reward, pleasure and addiction. This may explain the decreased addiction potential of modafinil compared to other stimulants.

Sodium oxybate (Xyrem) – The exact mechanism of action of sodium oxybate (Xyrem) is unknown. This medication, known chemically as the sodium salt of gamma-hydroxybutyrate (GHB), is similar to gamma-aminobutyric acid (GABA). However, there are distinct GHB receptors in the CNS, where GHB is believed to function as a neurotransmitter and cause marked CNS depression.

ii) FDA-approved indications – Both modafinil (Provigil) and sodium oxybate (Xyrem) are indicated for the treatment of excessive sleepiness associated with narcolepsy. Modafinil (Provigil) is also indicated for the treatment of excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) when used as an adjunct to continuous positive airway pressure (CPAP) treatment, and shift-worker sleep disorder (SWSD). Sodium oxybate (Xyrem) is also indicated for the treatment of cataplexy in narcolepsy.

Sodium oxybate (Xyrem) under the moniker of GHB attained notoriety in the 1980s as an illicit drug abused for drug-assisted sexual assault. In 2002, action by the U.S. Congress reclassified the drug as a schedule III product for treatment of narcolepsy. The FDA required a restricted distribution system, the Xyrem Success Program, as a condition for the 2002 approval to reduce the likelihood of diversion for illicit purposes. This program consists of exclusive distribution through a centralized pharmacy, a physician and patient registry, compulsory educational materials for both the physician and the patient, and a tracked method of shipping.

iii) Non-FDA approved indications – Modafinil (Provigil) is used for several conditions that are not approved by the FDA, including ADHD; fatigue associated with chronic diseases (cancer, Parkinson's disease, chronic fatigue syndrome, multiple sclerosis, fibromyalgia); fatigue associated with myotonic dystrophy, idiopathic hypersomnia, or due to antipsychotic or narcotic mediations; augmentation therapy for depression; cocaine dependence; schizophrenia; fatigue related to polio; and several others.

iv) Efficacy

Modafinil (Provigil)

- *Narcolepsy (FDA approved indication):* Four randomized double-blinded placebo controlled trials [US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000; Broughton 1997; Billiard 1994] reported statistically significant improvements in objective and subjective daytime sleepiness. The American Academy of Sleep Medicine rates modafinil as the "standard" of treatment for narcolepsy.
- *Excessive daytime sleepiness associated with OSAHS (FDA approved indication):* Three randomized double-blinded placebo controlled trials evaluated the efficacy of modafinil administered as an adjunct to CPAP treatment [Black 2005, Pack 2005, Kingshott 2001]. In the majority of the patients studied, there were statistically significant improvements (rated both objectively by providers and subjectively by the subjects) in daytime sleepiness.
- *Excessive daytime sleepiness associated with SWSD (FDA approved indication):* Two randomized double-blinded placebo controlled trials [Czeisler 2005, Rosenberg 2003] both showed statistically significant

improvement in objective and subjective measures of fatigue in patients during work-time shifts.

- *Depression (non-FDA approved indication)*: Two randomized double-blinded placebo controlled trials [Fava 2005, Frye 2005] reported statistically significant improvement in objective measures of global improvement. There were improvements in some (but not all) depression-specific rating scales. There was no evidence of increased manic emergence in patients with bipolar depression.
- *Multiple Sclerosis (MS) (non-FDA approved indication)*: One randomized double-blinded placebo controlled trial and one single blinded trial [Stankoff 2005, Rammohan 2002] evaluated efficacy of modafinil for fatigue associated with multiple sclerosis (MS). Stankoff et al showed no statistically significant difference in subjective measures of fatigue and daytime sleepiness. However, Rammohan et al showed a statistically significant improvement in objective measures of fatigue and daytime sleepiness. The National MS Society's expert opinion guideline on management of multiple sclerosis fatigue recommends 200 mg of modafinil daily as a primary treatment of MS fatigue, once secondary causes of fatigue have been addressed.
- *Cocaine dependence (non-FDA approved indication)*: There are two randomized double-blinded placebo controlled trials evaluating use of modafinil to treat cocaine dependency [Dackis 2003, 2005]. One trial showed a statistically significant decrease in self-rated euphoria in treated patients versus placebo. The other trial reported a statistically significant increase in the number of patients who remained abstinent from cocaine abuse for greater than three weeks versus placebo.
- *Myotonic dystrophy (non-FDA approved indication):* Two randomized double-blinded placebo controlled trials [MacDonald 2002, Talbot 2003] showed statistically significant improvements in subjective measures of daytime sleepiness, fatigue, and improvements in subjective quality of life measures.

Sodium oxybate (Xyrem)

- *Excessive daytime sleepiness:* Three randomized, double-blinded placebo controlled trials [Black et al 2006, US Xyrem Multicenter Study Group 2002, 2003] supported the FDA new drug application of sodium oxybate (Xyrem) for excessive daytime sleepiness. All three trials statistically significant improvements in subjective measures of daytime sleepiness with sodium oxybate compared to placebo; in some cases improvements approached normal values. Improvements in sleep quality, alertness, and concentration were also noted.
- *Narcolepsy associated with cataplexy:* Four randomized, double-blinded placebo controlled trials [US Xyrem Multicenter Study Group

2002, 2003, 2005, Scrima 1989] support the use of the drug for narcolepsy associated with cataplexy. All four trials reported statistically significant reductions in the number of cataplexy attacks ranging from 50% to 90%, compared to placebo.

- *Idiopathic hypersomnia:* Two open-label trials [Bastuji 1988, Laffont 1994] showed statistically significant reductions in the number of sleep attacks and daytime drowsiness in most patients treated. This disorder is clinically very similar to narcolepsy, and is diagnosed only through a sleep study by a sleep specialist.

2) Safety and Tolerability

a) ADHD Drugs

i) Black box warning

Stimulants: All the stimulants carry a black box warning of dependence, tolerance and abuse potential. The amphetamines carry a black box warning for sudden cardiac death. An FDA review of the adverse event reporting system concluded that the risk of sudden deaths was not greater than expected, given the large number of people taking the drug. Since the majority of the deaths occurred in children who had structural cardiovascular abnormalities, a warning against using any stimulant in such patients was added to labeling.

Non-stimulant: Atomoxetine (Strattera), which is mechanistically similar to some antidepressants, has a similar black box warning for suicidal ideation.

ii) Contraindications – The stimulants are contraindicated for use in patients with tics, a history of Tourette's syndrome, psychosis, or mania. Stimulants are also contraindicated in patients with significant cardiovascular disease and in patients who experience agitation. Stimulants and atomoxetine (Strattera) are contraindicated in patients who have ingested monoamine oxidase inhibitors (MAOIs) within the last 14 days, and in patients with glaucoma.

iv) Cardiovascular warnings – All the drugs in the ADHD class (both stimulant and non-stimulant) can raise blood pressure (on average by 2-4 mm Hg) and heart rate (on average by 3-6 beats per minute). All the products in the class carry a general warning for patients with underlying cardiac conditions.

v) Hepatotoxicity – Atomoxetine (Strattera) carries a bolded warning for liver injury in the package literature. In over two million treated patients, there have been two cases of significant liver injury. There is currently no recommendation by the manufacturer to monitor liver function in patients treated with atomoxetine.

vi) Decreased growth velocity – Early studies conducted with the stimulants showed a relationship between drug treatment and decreased growth velocity. Decreases in height can range from 0.7 to 1.9 cm in treated patients versus control patients. Long-term studies show trends for treated

patients to catch up with non-treated peers. Labeling for all stimulant products contains strong warnings for continual evaluation of growth velocity in treated patients.

vii) Dermatological reactions – Methylphenidate transdermal system (Daytrana patch) can cause contact sensitization, which is characterized by erythema with an intense local reaction. Rechallenge with the transdermal system may cause skin eruptions, headache, fever and malaise. Data provided by the manufacturer of the transdermal system shows that up to 13% of patients treated with methylphenidate transdermal system may become sensitized to orally administered methylphenidate.

viii) Drug interactions

Stimulants: The stimulants have clinically relevant drug interactions with MAOIs, anticonvulsants, and antidepressants. The body's ability to eliminate the mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) can be significantly affected by drugs or foods that alkalinize or acidify the urine.

Non-stimulants: Atomoxetine (Strattera) can interact with drugs that inhibit CYP2D6, including paroxetine (Paxil, generics), fluoxetine (Prozac, generics), and quinidine (generics).

ix) Minor adverse events

Stimulants: General adverse events frequently reported during use with any stimulant include delayed sleep onset, headache, decreased appetite, and weight loss. Mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) have a high percentage of patients who experience irritability and insomnia.

Non-stimulants: Atomoxetine (Strattera) is associated with somnolence, nausea, and vomiting, particularly when dosages are titrated to maximum doses over a few days. Decreased appetite is less of a concern with the atomoxetine than with the stimulants. Patients unable to tolerate adverse effects of the stimulants are often started on therapy with atomoxetine. Atomoxetine is not a controlled drug and is not associated with the same potential for abuse and tolerance as the stimulants.

x) Tolerability

Discontinuation due to adverse effects: Approximately 1%-7% of patients will discontinue ADHD drugs due to adverse events. The most frequently noted adverse events causing discontinuation are irritability, headache, anorexia, nervousness, and agitation.

Persistence: One report [Kenner 2003] comparing the once daily stimulant formulations showed that patients taking methylphenidate OROS (Concerta) and mixed amphetamine salts ER (Adderall XR) took their medication more consistently than patients receiving methylphenidate 30% IR/70% ER (Metadate CD). Another report [Marcus

2005] showed that patients were more persistent with Concerta for longer time periods than methylphenidate IR (Ritalin, generics).

xi) Safety and tolerability conclusion – Major concerns with the stimulants include potential for abuse and tolerance, as well as the potential for sudden cardiac death in patients with underlying structural heart defects. Slowed growth velocity remains an issue with all stimulants. The methylphenidate transdermal system (Daytrana) can cause significant dermatological adverse events and sensitization that can preclude subsequent use of any methylphenidate product. Patients receiving a once daily stimulant may be more persistent with therapy than with IR stimulants.

b) Narcolepsy Drugs

i) Modafinil (Provigil)

Serious adverse events: Three cases of clinically important rashes, including Stevens-Johnson Syndrome (SJS), occurred with modafinil (Provigil) in clinical trials investigating use of the drug for ADHD in children. The FDA adverse event reporting system has received five reports of SJS or erythema multiforme in adults. The new drug application for modafinil (submitted under the trade name Sparlon) for ADHD was denied by the FDA due to these reports.

Addiction potential: Modafinil (Provigil) is a Schedule IV controlled drug. It has not been associated with producing withdrawal symptoms or tolerance.

Drug Interactions: Modafinil (Provigil) undergoes primarily hepatic metabolism; however, there are few clinically significant drug-drug interactions. Absorption of methylphenidate and dextroamphetamine may be delayed by approximately one hour when co-administered with modafinil. Concurrent administration with oral contraceptives containing ethinyl estradiol may result in an 18% reduction in peak concentrations of ethinyl estradiol, thus alternate forms of contraception should be considered in females of child-bearing age.

General adverse events: In the six randomized double-blinded placebo controlled trials performed to obtain FDA approval, the most commonly reported treatment emergent adverse events included headache (34% with modafinil vs. 23% with placebo), nausea (11% with modafinil vs. 3% with placebo), nervousness (7% with modafinil vs. 3% with placebo), and insomnia or anxiety (5% with modafinil vs. 1% with placebo). The percentage of patients discontinuing therapy due to an adverse event was 8% with modafinil-treated patients vs. 3% with placebo-treated patients. Modafinil does not cause clinically significant increases in blood pressure or heart rate, and does not affect sleep architecture.

ii) Sodium oxybate (Xyrem)

Serious adverse events: Sodium oxybate (Xyrem) is a CNS depressant with a high potential for abuse. It carries a black box warning against concomitant use with alcohol or other CNS depressants. In the clinical trials used to gain FDA approval, two deaths were reported due to drug overdoses from ingestion of multiple drugs. Multiple deaths have been reported in association with GHB use, mostly in the setting of intentional abuse with other substances, where it is difficult to determine the exact doses used.

Addiction potential: The drug has demonstrated abuse potential given its properties as a psychoactive drug. A wide range of psychoactive effects have been reported, including dose-dependent sedation/hypnosis.

Drug interactions: Concomitant use of sodium oxybate (Xyrem) with barbiturates, benzodiazepines, and centrally acting muscle relaxants results in additive CNS and respiratory depression. One case report of sodium oxybate taken with methamphetamine resulted in seizure. Use with opioid analgesics and ethanol may result in respiratory depression.

General adverse events: In clinical trials enrolling over 700 patients with narcolepsy, the most commonly reported adverse events were headache (22%), nausea (21%), dizziness (17%), somnolence (8%), vomiting (8%), and enuresis (7%). In these trials, 10% of patients discontinued sodium oxybate (Xyrem) therapy due to adverse events (compared to 1% with placebo), most commonly due to nausea, dizziness, or vomiting (each occurring with a 2% incidence).

3) Other Factors

a) ADHD Drugs

i) Pregnancy/Lactation – All of the ADHD drugs are rated as pregnancy category C. The amphetamines and atomoxetine (Strattera) are excreted in breast milk. It is not known whether methylphenidate products are excreted in breast milk.

ii) Pediatrics – The FDA has approved the use of the ADHD drugs in patients down to the age of six years. Dextroamphetamine (Dexedrine, Dextrostat, generics) is labeled for use in patients as young as three years of age.

iii) Renal and hepatic dysfunction – Dosage adjustments are not required for any of the ADHD drugs in patients with renal failure. In patients with hepatic impairment, only atomoxetine (Strattera) requires dosage adjustment.

iv) Dosage formulations – The methylphenidate transdermal system (Daytrana) is the only non-oral formulation in this class. Methylphenidate 30% IR/70% ER (Metadate CD), mixed amphetamine salts ER (Adderall XR), dexmethylphenidate SODAS (Focalin XR) and methylphenidate SODAS (Ritalin LA) are capsule formulations that can be opened and sprinkled on

food for patients with swallowing difficulties. Methylphenidate IR (Methylin) is available in an oral solution and chewable tablets.

v) One survey [Wilens 2004] of students taking stimulant medications for ADHD treatment reported that 22% of patients escalated doses, with 10% escalating doses specifically for euphoric effects. Also of note, 11% of the students sold their medication to peers. Another survey [Teter 2006] of college students taking stimulant medication found that mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) were the most frequently abused products. A concerning finding was that the stimulants were crushed and snorted for their euphoric effects. Respondents also used the stimulants for weight loss and to increase concentration for studying.

vi) MTF provider opinion and clinical coverage: A total of 214 MTF providers responded to an opinion survey. All responders desired the availability of a long-acting methylphenidate product; providers specifically preferred methylphenidate OROS (Concerta). Providers prescribed Concerta more frequently than mixed amphetamine salts ER (Adderall XR) or atomoxetine (Strattera) when initiating therapy. However, providers requested availability of both Adderall XR and atomoxetine as therapeutic options for patients intolerant of or not responding to methylphenidate products. A methylphenidate IR product was also requested. Providers were not familiar with and did not prescribe the methylphenidate transdermal system (Daytrana), dexmethylphenidate IR and SODAS (Focalin, Focalin XR), and methamphetamine IR (Desoxyn, generics).

Survey responders stated that in addition to the current BCF agents, most pharmacies stocked methylphenidate SR (Ritalin SR) and about half the pharmacies stocked atomoxetine (Strattera). The most requested non-formulary agent was atomoxetine, followed by long-acting methylphenidate 30% IR/70% ER (Metadate CD.)

vii) Other Factors Conclusion: All the products in the ADHD class are rated pregnancy category C. All the products are indicated for use in pediatric patients. The dose of atomoxetine (Strattera) must be adjusted in patients with hepatic insufficiency. There are multiple products available for patients who have difficulty swallowing a tablet or capsule. The stimulants have significant abuse potential. MTF providers desired availability of a long-acting methylphenidate product, preferably methylphenidate OROS (Concerta); an IR methylphenidate product; mixed amphetamine salts ER (Adderall XR); and atomoxetine.

b) Narcolepsy agents

i) Modafinil (Provigil): Modafinil (Provigil) has not been evaluated in patients older than 65 years of age or younger than 16 years of age. The dosage should be decreased in patients with severe hepatic impairment.

ii) Sodium oxybate (Xyrem): Sodium oxybate is primarily metabolized in the liver; patients with hepatic insufficiency require dosage reduction by 50%. No dosage adjustment is necessary in patients with renal insufficiency. There is no clinical trial experience with patients over the age of 65 or under 16 years of age.

ADHD and Narcolepsy Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.

2) There is no evidence to suggest a difference in efficacy between IR formulations of methylphenidate (Ritalin, generics), dextroamphetamine (Dexedrine, Dextrostat, generics), dexmethylphenidate (Focalin), and mixed amphetamine salts (Adderall, generics).

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the products. Methylphenidate 30% IR/70% ER (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.

4) Mixed amphetamine salts ER (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.

5) The efficacy of atomoxetine (Strattera) appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The methylphenidate transdermal system (Daytrana) can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Atomoxetine (Strattera) remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) Responders to a provider survey expressed a desire for availability of the following products to cover clinical needs: methylphenidate OROS, an IR methylphenidate product, mixed amphetamine salts ER, and atomoxetine.

12) The narcolepsy drug modafinil (Provigil) fills a unique niche in therapy as a wakefulness promoting agent.

13) The narcolepsy drug sodium oxybate (Xyrem) has a high incidence of adverse events, but fills a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. ADHD and Narcolepsy Agents – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the ADHD and narcolepsy agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The cost-effectiveness review was conducted on subclasses based on each agent's indication for treatment (ADHD or narcolepsy). Drugs evaluated in the ADHD subclass were further grouped by duration of action. This process of categorization left three subclasses:

1) A once daily use subclass of ADHD products including mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexmethylphenidate SODAS (Focalin XR), methylphenidate OROS (Concerta), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate SODAS (Ritalin LA), and methylphenidate transdermal system (Daytrana).

2) A multiple daily use subclass of ADHD products including mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), dexmethylphenidate IR (Focalin), methamphetamine IR (Desoxyn, generics), methylphenidate IR (Ritalin, generics), and methylphenidate sustained-release (Ritalin SR).

3) A subclass of drug products indicated for narcolepsy including mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), methylphenidate IR (Ritalin, generics), modafinil (Provigil), and sodium oxybate (Xyrem).

The choice of cost-effectiveness analysis for each subclass was based on the findings from the clinical effectiveness review. The results of the clinical review showed evidence of differences among the drugs in the once daily use subclass in regards to efficacy. However, there was insufficient evidence to conclude that the multiple daily use and narcolepsy subclasses differed based on efficacy, safety, tolerability, or clinical outcomes. In light of these conclusions, the cost-effectiveness analyses were conducted as follows: (1) cost-utility analysis of the once daily use subclass; (2) cost-minimization analysis of the multiple daily use subclass; and (3) cost-minimization analysis of the drugs indicated for the treatment of narcolepsy.

1) The cost-utility analysis compared the costs per quality-adjusted life year (QALY) among the once daily use products. The results showed methylphenidate OROS (Concerta) to be the most cost-effective agent in this subclass. The mixed

amphetamine salts ER (Adderall XR) and methylphenidate 30% IR/70% ER (Metadate CD) also performed well with similar cost-effectiveness ratios. Atomoxetine (Strattera) was cost-effective under a scenario assuming greater patient preference for a non-stimulant once daily use product. Dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) The cost-minimization analysis of the multiple daily use products compared the weighted average cost per day of treatment across all three points of service for each drug product. The results revealed that most products were cost-effective, with methylphenidate IR (Ritalin, generics) being the most cost-effective agent in this subclass. Dexmethylphenidate IR (Focalin) was less cost-effective than other agents in this subclass. Furthermore, the absence of a compelling clinical rationale for inclusion on the UF suggested dexmethylphenidate IR should be evaluated for non-formulary status.

3) The cost-minimization analysis for the drug products indicated in the treatment of narcolepsy compared the weighted average cost per day of treatment across all three points of service for mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), methylphenidate IR (Ritalin, generics), and modafinil (Provigil). Sodium oxybate (Xyrem) also was included and evaluated at its cost per day of treatment in the retail point of service only, since it is not available at the other points of service due to its controlled distribution system. The results showed that methylphenidate IR was the most cost-effective agent in the treatment of narcolepsy, followed closely by dexamphetamine IR and mixed amphetamine salts IR. Sodium oxybate and modafinil, although more costly per day of treatment relative to the other drugs in this subclass, possessed unique clinical advantages justifying their inclusion on the Uniform Formulary. Modafinil has a unique niche for wakefulness promotion in a variety of disorders (as described in the clinical review) and sodium oxybate has proven efficacy for narcolepsy complicated by cataplexy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of ADHD/narcolepsy drugs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion

1) Once daily ADHD agents: dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) Multiple daily use ADHD agents: dexmethylphenidate IR (Focalin) was not cost-effective relative to the other agents in the subclass.

Agents indicated in the treatment of narcolepsy:

1) Although modafinil (Provigil) and sodium oxybate (Xyrem) were more costly relative to the other agents in the subclass, they possessed unique clinical advantages relative to other agents indicated for the treatment of narcolepsy.

2) The UF scenario that included dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) as non-formulary under the UF best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS and was the most cost-effective UF scenario.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the cost-effectiveness conclusions stated above.

C. ADHD and Narcolepsy Agents – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and Narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate SR (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the UF and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), methylphenidate transdermal system (Daytrana) be classified as non-formulary under the UF.

D. ADHD and Narcolepsy Agents – Medical Necessity Criteria

Based on the clinical evaluation for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin) and dexmethylphenidate SODAS (Focalin XR), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), and dexmethylphenidate SODAS (Focalin XR):

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

4) No formulary alternative is available.

The P&T Committee noted that criterion #4 would apply only to the use of methylphenidate transdermal system (Daytrana) by patients who require treatment with a once daily methylphenidate product, but who are unable to take oral medication.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

E. ADHD and Narcolepsy Agents – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 3,000 patients out of approximately 175,000 unique utilizers at all three POS), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), or dexmethylphenidate SODAS (Focalin XR) on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for a non-formulary ADHD agent written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. ADHD and Narcolepsy Agents – Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that two once daily use products and one or more multiple daily use products should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that the BCF remain unchanged with mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin, generics) on the BCF. Concerta has high utilization due to current BCF status, is a methylphenidate product with a 12-hour duration, and was determined to be the most cost-effective once daily methylphenidate product. Similarly, Adderall XR has high utilization at the MTFs; is an amphetamine product with a 12-hour duration, and was cost-effective relative to the other agents in the subclass. Methylphenidate IR is extremely cost-effective, is available in a generic formulation, and allows for dose titration.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin) as the BCF selections in this class.

8. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MODAFINIL (PROVIGIL)

Modafinil (Provigil) is approved by the FDA for treatment of excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) when used as an adjunct to continuous positive airway pressure (CPAP) treatment, and excessive daytime sleepiness associated with shift-worker sleep disorder (SWSD). There are numerous off-label uses for the drug.

Modafinil (Provigil) accounted for approximately $24 million in DoD expenditures in FY 06. Given the rapid increase in use and expenditures, a DoD-specific analysis of modafinil utilization was performed. Among unique utilizers of modafinil, as many as 44% of the total prescriptions appeared to be written for indications not supported by well-controlled studies with clinically meaningful endpoints that are published in refereed medical literature. Given the increasing use of modafinil for off-label indications not well established by the medical literature, the Committee agreed that a PA should be required for modafinil.

Taking into consideration the clinical review recommendation that modafinil (Provigil) require a PA, a threshold analysis was conducted to estimate the relationship between the administrative costs of conducting a PA policy and the cost-offset from reduced utilization of modafinil secondary to the policy. The results suggested that the administrative costs of a PA requirement for modafinil would not be cost-prohibitive.

The P&T Committee identified five off-label indications, in addition to the three FDA-approved indications, as supportable based on published clinical evidence or recommendations from nationally recognized expert organizations, based on guidelines from the TRICARE Policy Manual 6010.54 (August 2002) chapter 1 section 2.1 regarding coverage of unproven drugs, devices, medical treatments and procedures. With respect to the off-label uses, clinical evidence supports use of modafinil (Provigil) for augmentation of treatment for major depression, fatigue associated with multiple sclerosis (MS), augmentation of primary cognitive-behavioral therapy in acute rehabilitation of cocaine dependence, fatigue associated with myotonic dystrophy, and fatigue associated with idiopathic hypersomnia. Other off-label uses (e.g., in chronic fatigue syndrome, stroke rehabilitation, appetite suppression, Parkinson's disease and others) are supported only by case reports, uncontrolled trials, single-blinded trials, or chart reviews, which constitute insufficient evidence to establish efficacy and safety per TRICARE regulations. The PEC will continue to monitor the clinical literature on an ongoing basis for evidence that may justify revision of these criteria.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (Provigil) (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (15 for, 0 against, 0 abstained, 2 absent). PA approval would be good for one year. The P&T Committee noted that the PA is not intended to apply to modafinil (Provigil) use in Active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use.

1) Narcolepsy
2) OSAHS, only after adequate titration of CPAP treatment
3) SWSD, only in patients who work night shifts
4) MS, only after secondary causes of fatigue have been addressed

5) Myotonic dystrophy

6) Depression, only after primary therapy has failed and if the use of other stimulant augmentation is contraindicated

7) Idiopathic hypersomnia diagnosed by a sleep specialist

8) Cocaine dependence when approved by a DoD substance abuse program

9. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS)

Based on the following considerations, the P&T Committee agreed that a PA should be required for fentanyl patches (Duragesic, generics).

- Fentanyl, a strong opioid narcotic, can cause severe respiratory depression in patients who are not tolerant to opioids. Product labeling for fentanyl patches was strengthened in July 2005 following reports of serious adverse events and fatalities. Fentanyl patches are indicated for management of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. They should not be used for management of acute pain or short periods of opioid analgesia; post-op pain, including outpatient/day surgeries; mild pain; or intermittent pain.
- Warnings concerning safe use of fentanyl patches have been issued by various organizations, including the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices. On 31 July 2006, in response to reports of improper use of fentanyl patches, the Air Force established a policy restricting the prescription of fentanyl patches to pain specialists and other authorized providers and requiring drug utilization review by each facility. Pharmacists are required to review all fentanyl patch prescriptions to verify that:
  - Fentanyl is being prescribed for management of chronic pain.
  - The patient has already received opioid therapy, and requires a total daily dose at least equivalent to fentanyl 25mcg/h.
  - Fentanyl is NOT being prescribed for intermittent (prn) pain.
  - The patient is 2 years of age or older.
  - The patient is NOT receiving both fentanyl and potent CYP3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, or nefazodone).

- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by December 2006 will add the capability of "looking back" at a given patient's profile for the presence or absence of prescription fills for specific medications within a defined time period. This will allow the fentanyl PA to be targeted only to patients who may not be opioid-tolerant based on prior patterns of opioid use and limit the administrative impact of the PA on patients receiving fentanyl patches on a chronic basis.

COMMITTEE ACTION – Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following approval by the Director, TMA.

The P&T Committee agreed that the following general PA criteria should apply (15 for, 0 against, 0 abstained, 2 absent), based on requirements in product labeling. Patients meeting the automated PA criteria would not be required to have their providers submit any additional information. PA requirements will apply to each prescription (note, however, that a patient receiving fentanyl patches on a chronic basis would meet automated PA criteria for each prescription).

1) Automated PA criteria:

- Patient is likely to be opioid-tolerant based on the pattern of opioid use in the patient's profile during a defined "look-back" period

2) PA criteria if automated criteria are not met:

- Patient is likely to be opioid-tolerant based on prior opioid use not captured by PDTS (e.g., medications started on an inpatient basis or prescriptions filled outside the DoD pharmacy benefit) AND
- Patient requires a fentanyl patch for treatment of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time that cannot be managed by other means and NOT for management of acute pain or short periods of opioid analgesia, post-op pain (including outpatient/day surgeries), mild pain, or intermittent pain.

10. CLASS OVERVIEWS

Portions of the clinical reviews for each of the following classes were presented to the Committee: Topical Glaucoma Agents, Narcotic Analgesics, Angiotensin Receptor Blockers (ARBs), Growth Stimulant Agents, MAOI Antidepressants, 5-Alpha Reductase Inhibitors, 5-HT Receptor Agonists ("Triptans"), Antilipidemics II (LIP-2s), and (Proton Pump Inhibitors (PPIs).

The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the February 2007 or May 2007 meetings; no action is necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1430 hours on 15 November 2006. The dates of the next meeting are 13-15 February 2007.

_____signed_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	Pending approval	NA
Nov 06	ADHD	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	Pending approval	Pending approval
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			Pending approval	Pending approval
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. November 2006 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Insulin Human (rDNA origin) Inhalation Powder (Exubera; Pfizer/Nektar Therapeutics) inhaled insulin	Jan 06 ▪ For control of hyperglycemia in adults with type 1 diabetes in conjunction with long-acting ▪ For control of hyperglycemia in adults with type 2 diabetes either as monotherapy, or in combination with oral agents or long-acting insulin	No UF recommendation at this meeting. Consideration of UF status deferred until insulins are reviewed.
Fentanyl buccal tablet (Fentora; Cephalon) narcotic analgesic	Sep 06 ▪ Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. ▪ Patients considered opioid tolerant are those who are taking at least 60 mg of morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of hydromorphone daily, or an equianalgesic dose or another opioid for a week or longer.	No UF recommendation at this meeting. Consideration of UF status deferred until narcotic analgesics are reviewed; scheduled for Feb 07.
Posaconazole oral suspension (Noxafil; Schering-Plough) oral antifungal agent	Sep 06 ▪ Prophylaxis of invasive Aspergillus and Candida infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant recipients with graft-versus-hose disease, or those with hematologic malignancies with prolonged neutropenia from chemotherapy ▪ Treatment of oropharngeal candidiasis, including infections refractory to itraconazole and /or fluconazole	No UF recommendation at this meeting. Consideration of UF status deferred until oral antifungal medications are reviewed.
Drosperinone / estradiol 0.5 mg/1 mg (Angeliq; Berlex) hormonal replacement therapy	Sep 05 (launched Oct 06) Indicated in women who have a uterus for the: ▪ Treatment of moderate to severe vasomotor symptoms associated with the menopause. ▪ Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.	No UF recommendation at this meeting. Consideration of UF status deferred until hormonal replacement therapies are reviewed

Appendix C – Table 3. Table of Abbreviations

5-HT3	5-hydroxytryptamine-3
AAP	American Academy of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
CD	controlled delivery
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
CNS	central nervous system
CPAP	continuous positive airway pressure
DERP	Drug Effectiveness Review Project (state of Oregon)
DoD	Department of Defense
EE	ethinyl estradiol
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
GHB	gamma-hydroxybutyrate
IV	intravenous
IR	immediate release
LA	long acting
MAOI	monoamine oxidase inhibitor
MHS	Military Health System
MTF	military treatment facility
MS	multiple sclerosis
OTC	over-the-counter
OROS	osmotically controlled-release oral delivery system
OSAHS	obstructive sleep apnea/hypopnea syndrome
PA	prior authorization
PPI	proton pump inhibitor
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
QD	once daily
QID	four times daily
SED-2s	older sedative hypnotics
SJS	Stevens-Johnson Syndrome
SODAS	spheroidal oral drug absorption system
SR	sustained release
SWSD	shift worker shift disorder
TID	three times daily
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
VARR	voluntary agreements for TRICARE retail pharmacy rebates
XR	extended release

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2006

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the Food and Drug Administration. None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits, dasatinib (Sprycel), which is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. The Committee agreed that quantity limits were needed for dasatinib, based on the risk of discontinuation of therapy, the probability that dosage adjustments requiring changes in tablet strength will be needed, potential for drug interactions, and variable patient response to therapy and drug-related adverse effects. Other oral chemotherapy drugs also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in the TRICARE Mail Order Pharmacy (TMOP) Program of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days (not collective across strengths). In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days (not collective across strengths). (See page 14 of the P&T Committee minutes.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

The Committee agreed that a PA was needed for exenatide subcutaneous injection due to the potential for inappropriate use.

COMMITTEE ACTION: Based on exenatide's potential use for indications not covered by TRICARE (i.e., weight loss) and/or not supported by clinical evidence, the P&T Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that PA be required for exenatide. The criteria recommended by the P&T Committee incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 14-16 of the P&T Committee minutes for rationale and summary of PA criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: The Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that the PA for exenatide should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA). (See pages 14-16 of the P&T Committee minutes.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. THIAZOLIDINEDIONE (TZD) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the TZD drugs marketed in the United States. The drugs in this class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/ glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.

2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.

3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.

4) Safety and tolerability differences appear to be limited to the potential for more drug interactions with pioglitazone.

5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding – provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 1 abstained, 0 absent) that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride on the UF formulary was the most cost effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the TZD drugs, and other relevant factors, the P&T Committee voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 7A and 7B on pages 16-23 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (13 for, 1 opposed, 3 abstained, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/metformin to the BCF. (See paragraph 7E on page 23 of the P&T Committee minutes for rationale.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANT AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The drug class comprises: the four H2 antagonists, ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million in FY 2005, and is ranked 75th in MHS drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of gastroesophageal reflux disease, peptic ulcer disease, and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to proton pump inhibitors and H2 antagonists for stress ulcer prophylaxis.

Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that: (1) ranitidine was the most cost effective H2 antagonist; (2) two other H2 antagonists, famotidine and cimetidine, were shown to have similar relative cost-effectiveness compared to ranitidine; (3) nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, due to recent

availability of the generic version; and (4) misoprostol and sucralfate are available in generic versions and have an established niche in therapy for select patients.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained as formulary on the UF, and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 8A and 8B on pages 23-27 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations. (See paragraph 8E on page 27 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. ANTILIPIDEMIC I (LIP-I) AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the agents in the LIP-1 drug class. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. The individual drugs included in the LIP-1 class are listed below:

- *Statins*: atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release (Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor), and simvastatin (Zocor, generics)
- *Statin combination products*: atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)
- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

The Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that the following conclusions apply:

1) Across equipotent doses, the statins achieve similar % low density lipoprotein (LDL) lowering, with rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of achieving LDL lowering >55%.
2) Across equipotent doses, the statins achieve similar % high density lipoprotein (HDL) raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.
3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).
4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis [Zhou 2006].
5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.
6) In trials assessing the secondary prevention of CHD, beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).
7) In one trial assessing acute coronary syndrome patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg [PROVE-IT 2004].
8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.
9) There is no evidence that increases in liver function tests or minor adverse events (gastrointestinal disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.
10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.
11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles.
12) There is insufficient evidence to determine whether one statin is less tolerable than another.
13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.
14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct from that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP- I agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that (1) simvastatin could meet the vast majority of the needs of patients requiring low to moderate % LDL lowering agents (≤ 45%); (2) ezetimibe/simvastatin was the most cost-effective intensive % LDL lowering agent; (3) some low to moderate % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin); (4) of the remaining low to moderate % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share; (5) atorvastatin/amlodipine was considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service; and (6) the UF scenario that included the intensive % LDL lowering agents atorvastatin and ezetimibe/simvastatin on the UF was the most cost-effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin extended & immediate release, and ezetimibe be maintained as formulary on the UF, and that rosuvastatin and the combination product atorvastatin/amlodipine be classified as non-formulary under the UF. (See paragraphs 9A and 9B on pages 28-38 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:
"Our efforts to sustain the TRICARE benefit, and the TRICARE Rx benefit, require that MTF prescribers continue using simvastatin when that drug is clinically appropriate. I strongly encourage MTF commanders, doctors and pharmacists to maximize the use of simvastatin."

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of rosuvastatin and atorvastatin/amlodipine, and the conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) medical necessity criteria for the LIP-1 agents. (See paragraph 9C on pages 38-39 of the P&T Committee minutes for criteria

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) to recommend an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 9D on page 39 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost-effectiveness analysis, the P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/ simvastatin, and niacin extended release as the BCF selections in this drug class. (See paragraph 9E on page 40 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZO-DIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix D – Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction

Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

William Winkenwerder, Jr., M.D.
Date: 23 October 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes
16 August 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 15 August 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer (Pharmacy Consultant)
LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
Not Appointed	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer (Pharmacy Consultant)
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms. Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms. Julie Liss	DoD Pharmacoeconomic Center
Ms. Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms. Harsha Mistry	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
LTC Bret Kelly, MSC, USA	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Mr. Charles R. Brown	TMA/CMB
Mr. Vincent Calabrese	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. May Minutes Approval – Dr. William Winkenwerder, Jr., M.D., approved the minutes of the May 2006 DoD P&T Committee meeting on July 26, 2006.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the DoD P&T Committee regarding the June 29, 2006 BAP meeting. The Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Administrative Action: Quantity Limits for Tramadol Extended Release (Ultram ER) – Quantity limits apply to all tramadol-containing products, including new formulations, based on DoD P&T Committee recommendations made at the February 2005 meeting and subsequently approved by the Director, TMA, on 18 April 2005. The major potential concern with tramadol is safety (risk of seizure at higher than recommended doses); the potential for overuse or diversion may also exist. The Committee concurred with the specific quantity limits established for a new extended release formulation of tramadol (Ultram ER): 30 tablets per 30 days or 90 tablets per 90 days for all strengths, with quantity limits for the 200- and 300-mg tablets applied collectively. These limits were based on available strengths, dosing, titration, and maximum dose recommendations in product labeling (100-, 200-, and 300-mg extended release tablets initiated at 100 mg once daily and titrated up as necessary by 100-mg increments every five days to a maximum of 300 mg per day). The quantity limit is not collective with the immediate release formulations (tramadol 50 mg tablets and tramadol/acetaminophen 37.5/325 mg tablets) because of differences in strengths, Food and Drug Administration (FDA)-approved indications, and dosing recommendations. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TRICARE Mail Order Pharmacy (TMOP), and TRICARE Retail Pharmacy Network (TRRx) programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

C. Administrative Action: Removal of Carbinoxamine/Pseudoephedrine Drops from the Basic Core Formulary (BCF) – Like a number of older products, carbinoxamine combination products have been widely used, but were never approved by the FDA as safe and effective. On 8 June 2006, the FDA announced enforcement actions to stop manufacture of unapproved carbinoxamine-containing products due to safety concerns in children $\leq$ 2 years of age, and as part of ongoing FDA efforts to bring all unapproved products in line with provisions of the Food, Drug, and Cosmetic Act. Manufacturers of unapproved products containing carbinoxamine have been directed to cease manufacture over the next 30 to 90 days. One FDA-approved carbinoxamine 4 mg tablet and one 4 mg/5 mL oral solution will remain on the market, but no combination products. The Committee concurred with an administrative action removing carbinoxamine 1 mg / pseudoephedrine 15 mg per mL oral drops from the BCF. They did not feel that addition of another antihistamine/ decongestant combination to the BCF was warranted at the present time, pending future UF review of these medications.

D. UF Change Request Process – The P&T Committee discussed the process by which MTF healthcare providers could request that the DoD P&T Committee consider potential changes to the BCF, Extended Core Formulary (ECF), or UF, including changes to

medical necessity criteria for non-formulary medications, prior authorization criteria, or quantity limits. The P&T Committee agreed on three general process goals:

1) Requests should contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.

2) The process should address potential conflicts of interest and discourage pharmaceutical industry representatives from putting pressure on providers to submit requests.

3) The process should require review and concurrence by the local military treatment facility (MTF) P&T Committee.

A request form and supporting materials are currently under development.

E. Fentanyl Patch (Duragesic, generics) – The P&T Committee discussed various issues related to the use of fentanyl patches, including safety warnings from the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices; and the July 2006 Air Force policy on the use of fentanyl patches. Fentanyl, a strong opioid narcotic, can cause severe respiratory depression in patients who are not tolerant to opioids. Other safety issues include failing to remove old patches, unsafe disposal of old patches, application of heat to the patch site (e.g., heating pads, water beds), concurrent use of potent CYP3A4 inhibitors, conditions that affect respiratory function or affect metabolism of fentanyl, abuse, and diversion.

Product labeling for fentanyl patches was strengthened in July 2005 following reports of serious adverse events and fatalities. Fentanyl patches are indicated for management of *persistent*, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. They should not be used for management of acute pain or short periods of opioid analgesia; postop pain, including outpatient/day surgeries; mild pain; or intermittent pain.

F. Implementation Status of UF Decisions – The PEC briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August 2005. The Committee made the following observations:

1) Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.

2) Collective utilization of UF agents across all reviewed drug classes and points of service (MTF, TMOP, and TRRx) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 26% reduction in the use of non-formulary agents, including those classes where implementation has only just begun (July 2006).

3) Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.

4) Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).

5) For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 84% as projected, but the change in the use of non-formulary medications at mail (+1%) and retail (-14%) is significantly less.

6) It appears that more beneficiaries are electing to receive non-formulary medications through TMOP.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the FDA. None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed.

The P&T Committee reviewed one new drug for quantity limits. Dasatinib (Sprycel) is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia, with resistance or intolerance to prior therapy including imatinib (Gleevec). Dasatinib is available in 20-, 50- and 70-mg tablets which should not be crushed or cut. It is administered at a target dosage of 70 mg twice daily, but dosing can vary from 20 mg once daily to 100 mg twice daily, based on potential drug interactions, patient response, or drug-related adverse effects. Quantity limits were recommended for dasatinib due to the risk of discontinuation of therapy and the probability that dosage adjustments requiring changes in tablet strength will be needed, based on potential drug interactions, patient response to therapy, or drug-related adverse effects. Quantity limits also apply to other oral chemotherapy drugs, including imatinib, erlotinib (Tarceva), sorafenib (Nexavar), and sunitinib (Sutent), based on previous DoD P&T Committee recommendations and subsequent approval by the Director, TMA.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in TMOP of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days. In TRRx, the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days.

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus (DM) who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control. Pharmacologically, exenatide is an incretin mimetic agent that stimulates insulin production in the pancreatic islet cells when glucose levels are elevated, slows gastric emptying, and helps produce a feeling of satiety. Exenatide also reduces the secretion of glucagon, thus lowering elevated post-prandial blood glucose levels. It is given twice daily by subcutaneous injection, prior to the morning and evening meals. Exenatide should not be used as a

substitute for insulin in patients who need insulin, has not been studied in patients also using insulin, and is not indicated for use in patients with type 1 DM.

In clinical trials, exenatide decreased glycosylated hemoglobin A1c (HbA1c) by 0.7 to 1.1% (insulin typically decreases HbA1c by 1-2%). Also noted during clinical trials were reduced sulfonylurea requirements and reductions in weight (1.9 to 4.5 kg). From a safety standpoint, use of exenatide with a sulfonylurea may increase the risk of hypoglycemia, and the sulfonylurea dose may need to be reduced. Concurrent use of exenatide and metformin is relatively unlikely to cause hypoglycemia. Because it slows gastric emptying, exenatide may alter the rate and extent of absorption of oral drugs; drugs dependent on threshold concentrations for efficacy (e.g., antibiotics, contraceptives) should be taken at least one hour prior to exenatide. Exenatide is not recommended in patients with severe gastrointestinal (GI) disease, including gastroparesis, or in patients with severe/end stage renal disease. It is associated with GI adverse effects, including nausea, vomiting, and diarrhea; patients receiving exenatide in clinical trials also complained of significantly more jitteriness, dizziness, and headache than those receiving placebo.

Exenatide has achieved some notoriety as a weight loss medication (even in non-diabetic patients), an off-label use that is both not supported by clinical evidence and not covered by TRICARE. In addition, it appears likely that exenatide may be used in some patients with metabolic syndrome or "pre-diabetes," another off-label use not supported by clinical evidence. Based on results of a utilization study performed by the PEC, about 90% of Military Health System (MHS) patients who received a first prescription for exenatide from June 2005 to May 2006 had also filled a prescription for an oral antidiabetic drugs, blood glucose test strips, or both during the 180 days prior to starting exenatide (8,681 out of a total of 9,634 patients). In other words, about 10% of MHS patients starting exenatide appear unlikely to be diabetic, based on absence of prescription fills for either diabetic medications or blood glucose testing supplies during the six months prior to starting exenatide. While there may be alternative explanations for some of these cases, it appears that some of these patients are receiving exenatide as a weight-loss medication and/or in a setting of "pre-diabetes." Many health plans have PA requirements for exenatide, primarily based on its FDA indication.

The cost of exenatide ranges from $1250 to $2500 per year, depending on dose and pharmacy point of service. Exenatide prescription fills are increasing rapidly at retail network pharmacies, where most exenatide fills are dispensed; relatively few fills and a slower rate of increase are seen at TMOP or MTFs.

Based on the following considerations, the P&T Committee agreed that a PA should be required for exenatide:

- In the MHS, up to 10% of exenatide usage appears likely to be used for indications not covered by TRICARE and/or not supported by clinical evidence. The use of exenatide for weight loss may increase based on continued coverage in the lay press increasing familiarity with the medication. Overall, utilization of exenatide is increasing.
- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by December 2006 will add the capability of "looking back" at a given patient's profile for the presence or absence of prescription fills for specific medications within a defined time period. This will allow automation of some PA criteria, reducing

paperwork burden and cost (PA fees), and limiting the scope of the PA to those patients most likely to fail to meet the established criteria.

COMMITTEE ACTION – Based on its potential use for indications not covered by TRICARE and/or not supported by clinical evidence, the P&T Committee recommended that a PA be required for exenatide (14 for, 1 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (14 for, 1 against, 0 abstained, 2 absent). Patients meeting the automated PA criteria would not be required to have their providers submit any additional information and in all likelihood would not even be aware of the existence of the PA. PA approvals would be valid indefinitely.

1) Automated PA criteria:
   - Patient has received any oral antidiabetic agent in the last 120 days
2) PA criteria if automated criteria are not met:
   - Coverage is approved if the patients meets both of the following criteria:
     - Diagnosis of type 2 DM
     - Patient has not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea

7. THIAZOLIDINEDIONE DRUG CLASS REVIEW

The drugs in the thiazolidinedione (TZD) class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in MHS drug class expenditures.

A. TZD Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the TZD products currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) Efficacy for Glycemic Control

Rosiglitazone and pioglitazone and their fixed-dose combinations with metformin or

glimepiride are FDA-approved for treating patients with type 2 DM. The primary efficacy measures evaluated included HbA1c and fasting plasma glucose (FPG).

- *Monotherapy* – TZDs may be given as monotherapy, but are usually administered with other antidiabetic drugs, including metformin, sulfonylureas, or insulin. Placebo-controlled trials show that rosiglitazone monotherapy reduces HbA1c by 0.6% to 1.5% and FPG by 33 mg/dL to 55 mg/dL, while pioglitazone monotherapy reduces HbA1c by 0.7% to 1.2% and FPG by 36 mg/dL to 56 mg/dL.
    - *Head-to-Head Monotherapy Trials* – The only rigorously designed head-to-head clinical trial comparing rosiglitazone and pioglitazone monotherapy included 802 patients. The trial showed similar reductions in HbA1c after 24 weeks of therapy (0.6% with rosiglitazone vs. 0.7% with pioglitazone, p=0.129) and FPG (36 mg/dL with rosiglitazone vs. 33 mg/dL with pioglitazone, p=0.233). [Goldberg 2005]
    - *Meta-Analyses* – A meta-analysis of 23 placebo-controlled TZD monotherapy trials concluded that, when relatively equivalent doses of the TZD were compared, similar mean changes from baseline in HbA1c were reported: -0.90% (95% Confidence Interval [CI] -1.42% to -0.38%) with rosiglitazone 4 mg once daily (QD); -0.99% (95% CI -1.32% to -0.66%) with pioglitazone 30 mg QD. Similar point estimates and overlapping confidence intervals were reported for rosiglitazone 8 mg QD and pioglitazone 45 mg QD for reductions in both HbA1c and FPG. [Chiquette 2004]
- *Combination Therapy* – When a TZD is added on to another antidiabetic drug, greater reductions in HbA1c and FPG are seen than if the TZD is administered as monotherapy.
    - *Head-to-Head Combination Therapy Trials* – There is one head-to-head trial comparing the TZDs used in combination with the sulfonylurea glimepiride, which enrolled 91 patients. Similar changes in glycemic parameters from baseline were reported in both treatment groups. HbA1c decreased by 1.3% with rosiglitazone plus glimepiride vs. 1.4% with pioglitazone plus glimepiride; FPG decreased by 31 mg/dL in both groups. [Derosa 2004]
    - *Meta-analyses* – A meta-analysis of 15 clinical trials evaluating metformin, sulfonylurea or insulin plus a TZD compared to metformin, sulfonylurea, or insulin plus placebo concluded that when relatively equivalent doses of the TZDs were compared, similar mean changes from baseline in HbA1c were reported: [-1.05 (95% CI-1.2 to -0.9) with rosiglitazone 4 mg QD plus other antidiabetic drugs vs. -1.16 (95% CI -1.4 to -0.0) with pioglitazone 30 mg QD plus other antidiabetic drugs]. Similar reductions in HbA1c and FPG, with overlapping confidence intervals, were reported for rosiglitazone 8 mg QD plus other antidiabetic drugs vs. pioglitazone 45 mg QD plus other antidiabetic drugs. [Chiquette 2004]
- *Monotherapy and Combination Therapy* – A systematic review evaluating placebo-controlled trials with the TZDs used as either monotherapy or added on to other antidiabetic drugs reported an adjusted indirect comparison between

rosiglitazone and pioglitazone. Overall, there was no significant difference between the two drugs (adjusted mean difference, pioglitazone minus rosiglitazone, of -0.12% (95% CI -0.50 to 0.26)). [State of Oregon 2006]

Conclusion: Efficacy for Glycemic Control – The available evidence suggests that neither rosiglitazone nor pioglitazone is superior to the other in reducing HbA1c or FPG.

2) *Effectiveness for Prevention of Microvascular and Macrovascular Events*

For clinical outcomes, endpoints evaluated included microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular (e.g., cardiovascular disease, cerebral vascular disease, peripheral vascular disease) complications of type 2 DM, when available.

- *Microvascular Complications* – There are no clinical trials with either rosiglitazone or pioglitazone that evaluate the effects of long-term TZD therapy on prevention of microvascular complications. However, both TZDs reduce HbA1c, and reductions in HbA1c are correlated with a reduced risk of microvascular events, as previously shown in the United Kingdom Prospective Diabetes Study.
- *Macrovascular Complications* – Coronary heart disease is the major cause of mortality in diabetic patients, thus clinical trials evaluating cardiovascular outcomes are of importance when comparing the TZDs. There is one published trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), that evaluated the effects of pioglitazone on clinical outcomes in over 5,000 patients. After three years, there was no significant difference with pioglitazone added to other antidiabetic medications compared to placebo plus other antidiabetic medications in the primary composite outcome, which included both disease and procedure-related endpoints (i.e., myocardial infarction (MI), stroke, need for coronary artery bypass grafting, percutaneous coronary intervention or leg amputation). Overall, 21% of patient reached the primary endpoint with pioglitazone vs. 23% with placebo; p=0.095). However, a significant difference in favor of pioglitazone was reported in a secondary composite endpoint that only included disease-related endpoints (all-cause death, non-fatal MI and stroke); 11.6% with pioglitazone vs. 13.6% with placebo, p=0.027. The design of this trial has been debated, and the clinical applicability of these results is limited. There are no completed trials with rosiglitazone evaluating clinical outcomes, although two trials (ADOPT and RECORD) are underway.

Conclusion: Effectiveness for Prevention of Microvascular and Macrovascular Events – Due to the absence of published trials with rosiglitazone and design limitations of the one published trial with pioglitazone PROACTIVE, there is insufficient evidence to determine whether one TZD is superior to the other in preventing the clinical complications of diabetes.

3) *Safety and Tolerability*

- *Hypoglycemia* – One meta-analysis compared the differences in the incidence of hypoglycemia between rosiglitazone and pioglitazone. The pooled risk

differences were compared with each drug vs. placebo, and the results were similar for each TZD; rosiglitazone risk difference vs. placebo 3% (95% CI 0% to 5%) and pioglitazone risk difference vs. placebo 2% (95% CI -1% to 4). [State of Oregon 2006]

- *Edema* – Mild to moderate edema has been reported with the TZDs and appears to be dose-related. One meta-analysis reported the pooled risk difference for the incidence of edema with the TZDs in placebo-controlled trials. The pooled risk difference compared to placebo was similar between the two TZDs: rosiglitazone 4% (95% CI 2% to 5%), pioglitazone 4% (95% CI 2% to 7%). [State of Oregon 2006]
- *Heart Failure* – Both rosiglitazone and pioglitazone have been linked to development of heart failure; neither are recommended for use in patients with New York Heart Association Class III or IV heart failure Product labeling for both rosiglitazone and pioglitazone are similar regarding warnings for fluid retention, which may lead to or worsen heart failure. The highest risk occurs when a TZD is used in combination with insulin. A retrospective review using a large health plan database found no difference between the two TZDs in the development of heart failure in a cohort of over 28,000 patients: rosiglitazone 2.39% vs. pioglitazone 1.63%; p=0.091. [Delea 2003]
- *Weight Gain* – Both TZDs cause statistically significant increases in body weight from baseline. The effect on body weight appears similar between TZDs, as evidenced by the results from head-to-head clinical trials – mean weight gain of 1.6 kg with rosiglitazone vs. 2.0 kg with pioglitazone – and published meta-analyses showing similar weight gain (about 3 kg with each TZD, with overlapping confidence intervals).
- *Hepatotoxicity* – Clinical trials for both TZDs report an incidence <1% for elevations in ALT three times the upper limit of normal. Both TZDs carry similar labeling regarding monitoring of liver enzymes.
- *Blood Pressure* – An association between TZD use and small but statistically significant reductions in blood pressure has been reported. There is insufficient information at this time to determine whether the blood pressure effects are different between rosiglitazone and pioglitazone.
- *Hematologic Effects* – Reductions in hemoglobin and hematocrit have been reported with both TZDs. This may be due to an increase in plasma volume rather than a decrease in red cell mass. The clinical significance of these hematologic effects is unknown.
- *Macular Edema* – An association between TZD use and macular edema has been reported in the literature. GlaxoSmithKline issued a “Dear Doctor Letter” on January 5, 2006 regarding the association of rosiglitazone with new onset and worsening macular edema. Takeda, the manufacturer of pioglitazone, disputes the occurrence of this adverse effect and has not issued a similar warning.
- *Drug-Drug Interactions* – The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, due to metabolism of the former by CYP3A4

enzymes. However, the clinical significance of the drug-drug interactions with pioglitazone may be counterbalanced by the availability of multiple metabolic pathways. Of note, use of pioglitazone with oral contraceptives containing ethinyl estradiol and norethindrone has resulted in reduced plasma concentrations of both hormones by 30%, which could result in decreased contraceptive efficacy. The clinical significance of this interaction is unknown, and no dosage adjustments are required in the package labeling for pioglitazone.

- *Withdrawal Due to Adverse Effects* – Drug discontinuations due to adverse effects were similar for rosiglitazone and pioglitazone in one head-to-head monotherapy trial: 2.7% for both TZDs [Goldberg 2005]. A systematic review reported withdrawal rates due to adverse effects of 4.9% with rosiglitazone vs. 4.8% with pioglitazone. [State of Oregon 2006]

Conclusion: Safety and Tolerability – The risk of heart failure, hypoglycemia, weight gain and edema do not appear to differ between rosiglitazone and pioglitazone. Hepatotoxicity has not been a concern with either TZD. There is insufficient evidence to determine whether the TZDs differ in respect to macular edema, changes in blood pressure, hemoglobin or hematocrit; only small changes from baseline in these parameters have been noted. The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, but this does not appear to have translated into a clinically significant difference between the two TZDs. The tolerability profiles of both TZDs appear similar, based on drug withdrawals due to adverse effects during clinical trials.

4) Effects on Lipid Parameters

The TZDs exhibit other actions that can have unintended consequences in type 2 DM patients. Treatment with rosiglitazone and pioglitazone can affect serum lipid parameters, including total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG). Diabetes is a coronary heart disease (CHD) risk equivalent, and most type 2 DM patients require treatment with lipid lowering therapy. CHD is the number one cause of death in type 2 DM patients.

- Two head-to-head trials (one as monotherapy, the other as add-on therapy with other diabetic medications) reported that rosiglitazone adversely affected the lipid panel, as reflected by increases in TC (by 15-16%), LDL (by 17-23%), and TG (by 15-18%). In contrast, pioglitazone showed a favorable effect on the lipid profile, as reflected by to increases in HDL (by 15%), and decreases in TG (by 12 to 22%). However, these two head-to-head trials differed in the reported results for the effect of pioglitazone on TC and LDL. Goldberg et al (2005) showed an increase in TC (6%) and LDL (16%), while Derosa et al (2003) showed a reduction in TC (by 6%) and LDL (by 12%).
- Two meta-analyses [Chiqeutte 2004 and Canada 2002] concluded that rosiglitazone therapy resulted in increases in TC (10-21%), LDL (7-15%), and HDL (2-3%), but did not affect TGs. Pioglitazone increased HDL (2-5%) and reduced LDL (0.4 to 0.5%). Reductions in TG were more pronounced with pioglitazone, but a statistically significant difference was noted only for

pioglitazone in the Canadian analysis. Both TZDs were associated with modest increases in HDL (by 2-5%); the marked difference between rosiglitazone and pioglitazone seen in the two head-to-head trials is not as noticeable in the two meta-analyses.

Conclusion: Effects on Lipid Parameters – Results from two head-to-head clinical trials and two meta-analyses that assessed the lipid effects with TZDs vary, but are mostly consistent with the results of the head-to-head monotherapy trial. [Goldberg 2005] Pioglitazone appears to have a more favorable effect on lipid parameters than rosiglitazone. The clinical significance of this difference has yet to be determined.

5) *Other Factors*

- Rosiglitazone is dosed either once or twice daily, while pioglitazone is dosed once daily.
- Rosiglitazone binds primarily to peroxisome proliferator-activated receptors (PPARs) gamma receptors, while pioglitazone binds to both PPAR gamma and alpha receptors; differences in receptor binding are theorized to account for differences in the effects on lipid parameters.
- There are no differences in the product labeling for the two TZDs for FDA-approved indications, contraindications, and use in special populations.
- Neither rosiglitazone nor pioglitazone are indicated for use in the pediatric population, in pregnancy, or while breast feeding.
- A survey of MTF providers revealed a split opinion as to whether the TZDs were therapeutically interchangeable, with half of the respondents favoring pioglitazone due to once-daily dosing and lack of detrimental effect on lipids, and the other half voicing no preference.

Conclusion: Other factors – There are only minor differences in terms of other factors for the TZDs. MTF provider opinion is split between preferring pioglitazone and no preference between the two.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.
2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.
3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.
4) Safety and tolerability differences appear to be limited to a possibly greater potential for drug interactions with pioglitazone.
5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding; provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. TZD Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the TZDs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Given the evidence-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the TZDs differed in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of type 2 DM, two cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of the agents within the TZD class.

1) The first CMA evaluated the agents based on their total weighted average cost per day of treatment, which was derived from their submitted prices for UF condition sets (1 of 1 TZD agent on the UF or 1 of 2 TZD agents on the UF) and their utilization history. The results of this analysis revealed that pioglitazone was more cost-effective compared to rosiglitazone for a 1 of 1 position on the UF, whereas rosiglitazone was more cost-effective compared to pioglitazone for a 1 of 2 position on the UF.

2) The second CMA evaluated the agents under various UF scenarios which placed one or more agents on the UF. In this analysis, all viable UF scenarios were considered. The various UF scenarios were evaluated on their projected post-decision total weighted average cost per day of treatment. The results of this analysis showed that the UF scenario that included both agents on the UF to be the most cost-effective.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the budget impact analysis (BIA) was to assist the Committee in determining which group of TZDs best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS.

Cost Effectiveness Conclusion – Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included both of the TZD agents and their associated combination products on the UF best achieved this goal when compared to other more restrictive alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios. The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the TZD cost analysis presented by the PEC. The P&T Committee concluded that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin,

pioglitazone/metformin, and rosiglitazone/glimepiride on the UF was the most cost effective UF scenario considered.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TZD agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstention, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF.

C. TZD Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. TZD UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. TZD Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that no more than one parent TZD, with or without its associated combinations, should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that rosiglitazone and rosiglitazone/metformin be maintained on the BCF. The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF.

COMMITTEE ACTION – The P&T Committee voted (13 for, 1 opposed, 3 abstention, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/ glimepiride to the BCF.

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANTS

This drug class is comprised of the four H2 receptor antagonists (H2 antagonists), ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million dollars in FY 2005, and is ranked approximately 75th in MHS drug class expenditures. More than 440,000 prescriptions for these medications are filled annually in the MHS, based on prescription data from July 2005 to June 2006.

A. H2 Antagonists & Other GI Protectants Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR, 199.21 (e)(1).

1) Efficacy

- *H2 Antagonists and GI Indications* – All four of the H2 antagonists have been

shown in numerous clinical trials to reduce gastric acid pH, particularly after a meal. They are all effective when used before meals to reduce reflux symptoms associated with food or exercise. Although largely replaced by proton pump inhibitors (PPIs) in clinical practice, H2 antagonists may still play a role in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and *H. pylori* infections. A 1997 drug class review conducted by the Department of Veterans Affairs, as well as the 1999 American College of Gastroenterology guidelines for the treatment of GERD, concluded that, although there are differences in the potency, duration of action and onset of action, H2 antagonists may be used interchangeably at equivalent doses. A search of the literature since 1999 yields little additional clinical literature concerning the H2 antagonists and does not change this conclusion.

- *H2 Antagonists and Non-GI Indications* – Cimetidine is distinct from the other H2 antagonists in that it has evidence to support use in non-GI conditions based both on its histamine-blocking characteristics and its apparent immunomodulating effects. Non-GI uses for cimetidine are numerous, and include treatment of chronic idiopathic urticaria, adjunctive treatment of cancer or herpes virus infections, and intermittent porphyria.
- *Sucralfate* – Sucralfate does not affect gastric acid pH, but is thought to act by forming a non-absorbable physical barrier over mucosal ulcerations. At least ten clinical trials addressing the treatment of both gastric and duodenal ulcers (all conducted in the 1980s) reported similar healing rates with sucralfate compared to cimetidine or ranitidine. Overall, sucralfate appears to be as effective and safe as the H2 antagonists for treating duodenal and gastric peptic ulcers, but it is only approved for treating duodenal ulcers. One landmark clinical trial comparing intravenous (IV) ranitidine with nasogastric sucralfate reported benefits for use in stress ulcer prophylaxis in the intensive care setting, where it may offer an advantage over IV use of the H2 antagonists, due to a reduced potential for development of aspiration pneumonia. Sucralfate should be reserved for mild cases of esophagitis only. As with the H2 antagonists, the popularity of sucralfate has diminished due to availability of PPIs.
- *Misoprostol* – Misoprostol is a synthetic prostaglandin analog that inhibits gastric acid secretion by directly stimulating parietal cells. It also appears to function as a mucosal protective agent. The drug is effective as an adjunctive medication to reduce GI events associated with non-steroidal anti-inflammatory drug (NSAID) use, and has been shown to significantly reduce the risk of NSAID-associated serious GI complications and symptomatic ulcers by about 40-60%. Non-GI (off-label) uses of misoprostol are primarily gynecological in nature. A review of MHS utilization patterns, based on quantities dispensed and the age and gender of patients receiving misoprostol, confirms that the overwhelming majority of misoprostol usage in DoD is for treatment of GI conditions.

2) Safety and Tolerability

- *H2 Antagonists* – There are no major differences between the four H2 antagonists with respect to safety and tolerability, with the exception of a greater potential for

drug interactions with cimetidine. Cimetidine inhibits cytochrome P450 enzymes, and is associated with several clinically significant drug interactions when administered concomitantly with other drugs metabolized via the CYP450 pathway, including theophylline, phenytoin, quinidine, nifedipine, amitriptyline, and warfarin. Labeling for all four H2 antagonists contains warnings concerning an association of H2 antagonist use with necrotizing enterocolitis in the fetus or neonate. All four are associated with minor complaints of nausea, vomiting, diarrhea or constipation.

- *Sucralfate* – The major safety concern with sucralfate is the risk of seizures due to aluminum absorption in patients with impaired renal function. There are reports of bezoar development in patients with gastroparesis. Constipation develops in about 3% of patients receiving sucralfate, and complaints of metallic taste and diarrhea are frequent. The aluminum component of sucralfate may interact with antacids.
- *Misoprostol* – A Cochrane review addressing adverse events found that significantly more patients receiving misoprostol vs. placebo withdrew from therapy due to adverse effects, primarily diarrhea, abdominal pain, and nausea [Rostom 2004]. Diarrhea occurs in 13% to 40% of patients. It is dose-related, occurs early in treatment, usually resolves with continued treatment, and can be minimized with administration with meals and at bedtime and avoidance of magnesium-containing antacids. Abdominal pain is reported in 7% to 20% of patients. Misoprostol is rated pregnancy category X, and is contraindicated in women of child-bearing age unless the benefits exceed the risks.

3) Other Factors

- *Dosing* – The four H2 antagonists exhibit minor differences in potency, duration of action, onset of action, and frequency of dosing. Cimetidine requires twice daily to four times daily dosing, while the remaining three H2 antagonists can be dosed once to twice daily.
- *Available formulations* – All four H2 antagonists are available in tablet and liquid dosage formulations. The available dosage formulations for sucralfate include a tablet and oral suspension, while misoprostol is only available in a tablet. Ranitidine is also available in a gel-filled capsule, granule, and effervescent tablet.
- *Utilization* – Of the six drugs included in the class, the H2 antagonists account for over 90% of the prescriptions written in the MHS for this drug class. Ranitidine is the most widely prescribed H2 antagonist in the MHS, accounting for 67% of all H2 antagonist prescriptions, followed by famotidine (22%), cimetidine (8%) and nizatidine (3%).
- *Pediatrics* – Ranitidine and famotidine are indicated for use in children as young as two years of age; nizatidine is indicated in children older than 11 years, and cimetidine is indicated for use in children older than 15 years of age.
- *Pregnancy* – The four H2 antagonists and sucralfate are rated as pregnancy category B. Misoprostol is rated as pregnancy category X.

Overall Clinical Effectiveness Conclusion - The Committee concluded that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of GERD, peptic ulcer disease and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for NSAID-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to PPIs and H2 antagonists for stress ulcer prophylaxis.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. H2 Antagonists & Other GI Protectants Relative Cost Effectiveness

In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

A simple cost analysis was employed to assess the relative cost-effectiveness of the agents within the H2 antagonist/GI protective therapeutic class. The agents within this class were evaluated on their weighted average cost per unit. The results of the cost analysis showed ranitidine to be the most cost effective H2 antagonist. A sole source joint DoD/VA contract is currently in place for ranitidine. The other generic H2 antagonists were shown to have similar relative cost-effectiveness compared to ranitidine, with the exception of nizatidine. Not surprisingly, nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, since a generic version has only recently become available. In regards to misoprostol and sucralfate, both of these agents are available in generic versions and have a niche place in therapy for select patients.

Conclusion – The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the H2 antagonists and other

GI protectants cost analysis presented by the PEC. The P&T Committee concluded that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the H2 antagonists and other GI protectants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF and that no agents from this class be classified as non-formulary under the UF.

C. H2 Antagonists & Other GI Protectants Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. H2 Antagonists & Other GI Protectants UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. H2 Antagonists & Other GI Protectants BCF Review and Recommendations – The P&T Committee had previously determined that one or more agents in this class should be considered for addition to the BCF. Currently, ranitidine (Zantac, generics) is on the BCF, with the effervescent tablet and gel-filled capsule formulations specifically excluded. The committee agreed that ranitidine should remain on the BCF. Since the gel-filled capsule and effervescent tablet dosage formulations were shown to be 19 to 64 times more costly per unit than generic ranitidine without offering any substantial increase in clinical effectiveness, the P&T Committee agreed that the gel-filled capsule and effervescent tablet formulations should continue to be excluded from the BCF.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations.

9. ANTILIPIDEMIC AGENTS 1 DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents I (LIP-1) agents. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. On average, during a twelve month period from July 2005 and ending June 2006, there were approximately 975,000 unique utilizers per quarter. Individual drugs in the LIP-1 class are listed below:

- *Statins*. atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release(Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor, generics), and simvastatin (Zocor, generics)
- *Statin combination products*. atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)

- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

A. LIP-1 Relative Clinical Effectiveness Review:

Information regarding the safety, effectiveness, and clinical outcomes of the LIP-1 agents was considered. The Committee's review focused primarily on the agents' ability to lower LDL concentrations, to raise HDL concentrations, and to reduce clinical outcomes including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and need for revascularization. Differences in the agents' effect on triglyceride concentrations, and benefits in treating non-cardiovascular conditions were not assessed in detail. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

1) Efficacy for %LDL lowering and %HDL raising

Endpoints: The differences between the statins in terms of %LDL lowering and %HDL raising were assessed. Elevated LDL concentrations and low HDL concentrations are both strong independent risk factors of CHD.

%LDL Lowering:

- The primary action of the statins is to reduce elevated LDL concentrations, which is the main target of cholesterol-lowering therapy recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. LDL reduction occurs in a dose-dependant fashion with the statins. However, increasing a statin dose provides only an additional 5 to 6% LDL lowering.
- Data obtained from the individual statin product labeling and clinical trials was used to compare differences in the agents' ability to lower LDL. The statins were divided into two groups: the low to moderate group can achieve ≤45% LDL lowering, and the intensive group can achieve >45% LDL lowering. (See Appendix E)
- The following statins are considered low to moderate %LDL lowering statins: all doses of fluvastatin, fluvastatin extended release, pravastatin, lovastatin, lovastatin extended release, atorvastatin 10 and 20 mg (as well as corresponding Caduet doses which include atorvastatin 10 or 20 mg), simvastatin 10, 20, and 40 mg, ezetimibe/simvastatin 10/10 mg, and rosuvastatin 5 mg.
- The following statins are considered intensive %LDL lowering statins: atorvastatin 40 and 80mg (as well as corresponding Caduet doses which include atorvastatin 40 and 80 mg), rosuvastatin 10, 20, and 40 mg, simvastatin 80 mg, and ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg.
- When equipotent doses are used, the statins achieve similar %LDL lowering (e.g., atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg all attain 41 to 45% LDL lowering). Rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg are the only statins capable of attaining >55% LDL lowering.
- Based on a previous model constructed by the PEC that evaluated National Health and Nutrition Examination Survey data, 80 to 85% of the DoD population

requiring a statin is expected to attain their LDL goal on simvastatin doses ≤40mg. Simvastatin is the highest utilized statin in the DoD. (See Figure 1).

%HDL Raising:

- The primary clinical use of the statins is to reduce elevated LDL concentrations; however beneficial effects on HDL are also seen.
- Evidence from published trials and product labeling support the conclusion that HDL generally rises in a dose-dependent fashion, however all statins show a plateau and drop-off of HDL raising effect as the highest doses are approached. For example, atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg can achieve an 8 to 9% increase in HDL concentrations, but at doses of atorvastatin 80 mg and ezetimibe/simvastatin 10/40 mg, only achieve a 5-6% increase in HDL.
- The Committee commented that other drugs that primarily target HDL are available (e.g., niacin, fibrates, bile acid resins), and that providers should choose a drug other than a statin if the primary goal is to raise HDL concentrations. Currently the most potent option for raising HDL is niacin.

2) *Efficacy for clinical outcomes:*

Endpoints: The main clinical endpoints used to evaluate differences in statin efficacy include all-cause mortality, cardiovascular mortality, MI, stroke, and need for revascularization. Numerous clinical trials have shown the benefits of statin therapy on reducing cardiovascular events. However, differences in clinical outcomes between the statins are difficult to compare, due to widely varying patient populations evaluated, vaguely defined endpoints, and comparison of non-equipotent statin doses.

Meta-analyses:

- There are no head-to-head trials comparing equivalent doses of statins that evaluate differences in mortality or other clinical outcomes. One meta-analysis (Zhou 2006) evaluated the differences between low to moderate doses of atorvastatin, simvastatin, and pravastatin in reducing mortality or cardiovascular events. Eight clinical trials (comprising both primary and secondary prevention trials) met the criteria for inclusion in the analysis. An adjusted indirect comparison was calculated.
- For all comparisons between the three statins (e.g., atorvastatin vs. pravastatin, atorvastatin vs. simvastatin, and simvastatin vs. pravastatin), there was no significant difference between the drugs in all-cause mortality, major coronary events (fatal CHD and nonfatal MI), cardiovascular death (coronary and cerebrovascular death), and major cardiovascular events (stroke); ($p>0.05$ for all comparisons).

Efficacy for primary prevention of CHD: Primary prevention trials consist of patients without clinically evident CHD. Beneficial effects on clinical outcomes for primary prevention of CHD have been noted with atorvastatin 10 mg (ASCOT-LLA and CARDS trials), lovastatin 20 to 40 mg (AFCAPS, TexCAPS trials), pravastatin 40 mg (WOSCOPS), and simvastatin 40 mg (HPS).

Efficacy for secondary prevention of CHD: Secondary prevention trials include patients with pre-existing cardiovascular disease, such as prior MI, or prior revascularization procedures. In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg (GREACE, TNT), lovastatin 40 to 80 mg (CABG), pravastatin 40 mg (LIPID, CARE), simvastatin 20 to 40 mg (4S), and fluvastatin 40 mg (administered bid) (LIPS).

- TNT: In the Treat to Target (TNT) trial, low dose atorvastatin 10 mg was compared to intensive dose atorvastatin 80 mg for 5 years in 10,000 patients with stable CHD. Intensive dose atorvastatin 80 mg was associated with significantly fewer patients reaching the primary composite outcome (which included non-fatal MI) vs. atorvastatin 10 mg (28.1% vs. 33.5%, $p<0.001$). There was no benefit of intensive dose atorvastatin when mortality was assessed as a single endpoint. The main conclusion was that reducing LDL to <100 mg/dL yielded incremental clinical benefits.
- IDEAL: In the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial, intensive dose atorvastatin 80 mg was compared to low to moderate dose simvastatin 20 to 40 mg. In contrast to TNT, intensive dose atorvastatin did not show a benefit in the primary composite endpoint (CHD death, hospitalized non-fatal MI, resuscitated cardiac arrest); (9.3% of atorvastatin patients reached the primary endpoint, vs. 10.4% of simvastatin patients; $p=0.07$).

Efficacy for ACS: A subgroup of secondary prevention trials focuses on ACS patients who can experience unstable angina and myocardial ischemia due to severe atherosclerotic plaque progression.

- PROVE-IT:
  - In the Pravastatin or Atorvastatin Evaluation and Intensive Therapy (PROVE-IT) trial, moderate dose pravastatin 40 mg was compared to intensive dose atorvastatin 80 mg for two years in over 4,000 recently hospitalized (< 10 days) patients with ACS. Significantly fewer patients receiving intensive dose atorvastatin 80 mg reached the primary composite endpoint (all cause death, MI, unstable angina requiring hospitalization, stroke) than moderate dose pravastatin 40 mg (22.4% vs. 26.3%, $p=0.005$).
  - The PROVE-IT trial provides evidence for immediate use of intensive dose statin in ACS patients. Additionally, a goal LDL <70 mg/dL should be considered in this population, as the ending mean atorvastatin LDL was 62 mg/dL vs. 95 mg/dL with pravastatin 40 mg.
  - It is unknown whether the beneficial results seen in the PROVE-IT trial would be duplicated if an intensive dose statin other than atorvastatin were evaluated, as no such studies have been published.
- PACT: In the Pravastatin in Acute Treatment (PACT) trial, pravastatin 20 to 40 mg did not show a reduction in coronary events vs. placebo, however statin administration was delayed for 24 hours and the trial duration was only 4 weeks.

- A to Z: In the Aggrastat to Zocor (A to Z) trial, no statistically significant reduction in coronary events was shown after 2 years in 4,000 ACS patients receiving early initiation (after one month) intensive dose simvastatin 40 to 80 mg vs. delayed initiation (after four months) of low dose simvastatin 20 mg. The long delay in statin administration, and not the individual statin evaluated, likely contributed to the negative results.

Rosuvastatin and ezetimibe/simvastatin: There are no published trials assessing the benefits of rosuvastatin on clinical outcomes; one large trial (JUPITER) is in progress. While there are no clinical trials specifically assessing the ezetimibe/ simvastatin formulation, there is evidence for clinical benefits of the simvastatin component from the Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) trials. There is no evidence to suggest that addition of ezetimibe to simvastatin would negate the clinical benefits of the simvastatin component.

3) *Safety and Tolerability*

Minor Adverse Events: The statins show similar common adverse event profiles. Data from the package insert suggests that the there is no evidence that minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another. These adverse effects appear dose-related.

Serious Adverse Events: The P&T Committee specifically focused on three main areas, elevated liver transaminases, proteinuria, and myotoxicity.

- Elevations in liver transaminases
  - Transient elevations of aspartate aminotransferase and alanine amino-transferase (AST/ALT) to greater than three times the upper limit of normal (ULN) can occur with all the statins. The incidence of elevations in transaminases with all the statins ranges from 0.3 to 3%, according to data from statin package inserts.
  - Increases in liver transaminases are more likely to occur with intensive dose statins vs. low to moderate dose statins. No evidence suggests that one statin is less likely than another to cause increased liver transaminases. There is no data to date that suggest elevations in ALT or AST are predictive of liver injury or long term hepatotoxicity.
- Proteinuria:
  - A retrospective analysis conducted by the FDA using preclinical NDA submissions reported that rosuvastatin 40 mg was associated with a 4 to 5% incidence of proteinuria. This was higher than the incidence reported with rosuvastatin doses $\leq$20 mg (1 to 4%), atorvastatin 10 to 80 mg (0.4% to 2%), simvastatin 20 to 80 mg (0.6% to 4%), or pravastatin 20 to 40 mg (0 to 1%). Limitations to this analysis include the use of spot urine dipstick testing rather than 24-hour urine collections, and the inclusion of data from both open label and placebo-controlled trials.

- Currently there are no requirements for monitoring of renal function with any of the statins. Due to the insufficient and poor quality evidence available at this time, it cannot be determined whether the incidence of proteinuria differs between the statins.

- Myotoxicity:
  - Varying definitions of the terms myotoxicity, myopathy, myalgia, myositis, and rhabdomyolysis make interpretation of the literature difficult. Rhabdomyolysis (symptoms of muscle pain accompanied by increased creatine kinase >10 times ULN, increased serum creatine and brown colored urine) occurs rarely with all the statins. Muscle symptoms with the statins appear to be dose related, and the intensive dose statins should be used with caution in patients at increased risk of myotoxicity.
  - One meta-analysis [CTTC 2004] reported an overall low incidence of rhabdomyolysis with simvastatin, pravastatin, lovastatin and fluvastatin that did not differ from placebo (0.023% with the statins vs. 0.015% with placebo).
  - Rosuvastatin was associated with an incidence rate of rhabdomyolysis two times higher than that of the other marketed statins after the first six months of therapy (hazard ratio 1.98; [95% CI 0.18 to 21.90] in one retrospective cohort study of health claims. [McAfee 2006]. This result was not statistically significant. The analysis excluded cerivastatin (Baycol), as it was removed from the market in 2001 due to a high risk of rhabdomyolysis.
  - Spontaneous adverse event reporting data from the FDA uses a reporting rate (number of spontaneous case reports for rhabdomyolysis per 1 million US prescriptions) instead of an incidence rate to determine differences in myotoxicity between the statins.
    - Cerivastatin had the highest reporting rate of rhabdomyolysis (72.88 per 1 million US prescriptions) based on data from the years 1988 to 2000 were analyzed, while it was still marketed.
    - Data from 2002 to 2004 show that the reporting rate of rhabdomyolysis is higher with rosuvastatin at 13.54 reports per 1 million prescriptions, compared to simvastatin (8.71), fluvastatin (3.44), lovastatin (2.76), atorvastatin (1.67) and pravastatin (1.63).
    - Limitations to the FDA reporting system include the lack of a control group, reliance on spontaneous reports which may not reflect the true incidence of an adverse event, and the low overall occurrence of rhabdomyolysis. FDA reporting rates are more useful to signal a trigger of concern, rather than to quantify relative risks between different drugs in a class.
    - Despite the differences between rosuvastatin and the other marketed statins in terms of reporting rates and incidence rates of myotoxicity, definitive conclusions cannot be drawn. However, concerns remain with rosuvastatin, particularly at intensive doses.

Drug interactions: Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles as they are not appreciably metabolized via the CYP3A4 system. Atorvastatin, lovastatin, and simvastatin do undergo CYP3A4 metabolism, which results in concerns of drug-drug interactions with amiodarone, diltiazem, "azoles", and other 3A4 metabolized drugs.

Special populations: Fluvastatin, pravastatin, and rosuvastatin are preferred in patients with renal or hepatic insufficiency, in HIV/AIDS patients, or in recipients of solid organ transplants, as they are not metabolized via the CYP3A4 system. These patient groups represent about 2 to 3% of the 9 million DoD beneficiaries.

Pediatrics: Pravastatin is approved by the FDA for use in children as young as 8 years old. Atorvastatin, simvastatin, and lovastatin are approved for use in children as young as 10 years with heterozygous familial hypercholesterolemia, a rare condition.

Pregnancy: All the statins are rated Pregnancy Category X, due to the risk of fetal malformations.

Tolerability: There is insufficient evidence to determine whether one statin is less tolerable than another due to a lack of meta-analyses or retrospective claims data evaluating this outcome and the varying results reported in head-to-head trials.

4) *Other Factors:*

Dosing titration and initiation: The statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg. Rosuvastatin 40 mg should only be initiated in patients failing to reach target LDL goals with rosuvastatin 20 mg.

Pleiotropic effects: The majority of the observational data suggesting pleiotropic benefit (e.g., beneficial effects other than LDL lowering) with the statins rests with atorvastatin. None of the pleiotropic markers (e.g., C-reactive protein,) have been shown consistently in randomized trials to cause CHD. There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects.

Markers of atherosclerotic progression: Rosuvastatin 40 mg was shown to cause plaque regression in the ASTEROID trial, and atorvastatin 80 mg was shown to slow the progression of plaque formation in the REVERSAL trial; both trials used intravascular ultrasound. Benefits on carotid intima media thickness have been shown with all the statins, except for rosuvastatin for which there is no published study.

5) *Efficacy and safety of ezetimibe:*

- Ezetimibe lowers LDL by a mechanism distinct from that of the statins, as it inhibits absorption of dietary cholesterol.
- Use of ezetimibe as monotherapy attains 15 to 19% LDL lowering and provides a treatment option for patients who are at risk for statin adverse events. Use of ezetimibe in combination with low to moderate statin doses provides greater LDL lowering (12 to 20% LDL lowering) vs. increasing the statin dose alone (5 to 6% LDL lowering).

- The combination of ezetimibe with a statin can be used to reach target LDL goals when statin monotherapy has failed, or to avoid the potential risks with using intensive statin doses as monotherapy.
- The proven benefits of cardiovascular outcomes seen with the statins have yet to be duplicated with ezetimibe, as there are no published trials.
- The most common adverse events with ezetimibe are abdominal pain, diarrhea and headache. The risk of elevations in liver transaminases is slightly increased when ezetimibe is combined with a statin (1.3 to 2%) vs. using statin monotherapy (0.4%). To date, there are only rare case reports of myotoxicity and rhabdomyolysis.
- Current MHS utilization and provider opinion support the need for ezetimibe in the MHS.

6) *Efficacy and safety of ezetimibe/simvastatin:*

- The combination of simvastatin with ezetimibe provides additional efficacy for LDL lowering.
- Doses of ezetimibe/simvastatin greater than 10/20 mg provide 45% to more than 55% LDL lowering, allowing a treatment option in those 15 to 20% of DoD patients unable to meet goal LDL with simvastatin alone.
- The efficacy profile of ezetimibe/simvastatin reflects that of the individual components.
- To date, no clinically important increases in safety issues, such as risk of liver transaminase elevation or myotoxicity have been reported.

7) *Efficacy and safety of niacin*

- Niacin is FDA-approved to raise HDL (along with fibrates). Niacin can raise HDL by 25%, and can be used as monotherapy or in combination with other drugs.
- Clinical outcomes including reduced stroke, MI, and all-cause mortality have been reported with niacin.
- The formulation of niacin extended release is associated with a reduced risk of GI adverse events and hepatotoxicity compared to niacin immediate release or over the counter forms of long-acting niacin (Slo-Niacin).
- The risk of myotoxicity and drug-drug interactions is reduced when niacin is used in combination with a statin, vs. using the combination of fibrates with a statin.
- The benefits of niacin extended release are limited to those patients who can tolerate the associated adverse effects (flushing and GI disturbances).

8) *Clinical issues with lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release*

- Lovastatin/niacin extended release is difficult to initiate and titrate, since it is available in a fixed dose formulation.

- Atorvastatin/amlodipine contains a statin in combination with the dihydropyridine calcium channel blocker amlodipine. Amlodipine (Norvasc) was designated non-formulary under the UF in August 05. No outcomes trials have specifically assessed the benefits of the fixed dose Caduet formulation, and there is no evidence to suggest improved adherence or additional LDL lowering with the combination.
- Lovastatin extended release does not offer additional LDL lowering or safety benefits over lovastatin. Unlike lovastatin, lovastatin extended release is available in a 60 mg tablet, but does not attain a >45% LDL lowering.
- Fluvastatin extended release has proven benefits from one trial assessing revascularization (LIPS) and is a non-CYP3A4 metabolized statin. However, it does not offer additional benefits over fluvastatin immediate release and does not attain a >45% LDL lowering.
- Overall, these drugs do not offer additional clinical benefits over the other antilipidemic agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

9) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering <45%, and also supported use of ezetimibe. Providers were also concerned with the safety profile of rosuvastatin.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Across equipotent doses, the statins achieve similar %LDL lowering, with rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of attaining LDL lowering >55%.
2) Across equipotent doses, the statins achieve similar %HDL raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.
3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).
4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis (Zhou 2006).
5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.
6) In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).

7) In one trial assessing acute coronary syndrome (ACS) patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg (PROVE-IT 2004).

8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.

9) There is no evidence that increases in liver function tests (ALT) or minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.

10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.

11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles,

12) There is insufficient evidence to determine whether one statin is less tolerable than another.

13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.

14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct to that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP-1 agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. LIP-1 Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the LIP-1 agents in relation to the effectiveness, safety, tolerability, and clinical outcomes of the other agents

in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). A series of cost-effectiveness analyses were used to determine the relative cost-effectiveness of agents within the LIP-1 therapeutic class.

For the high % LDL lowering agents (>45%, intensive) in the LIP-1 class (atorvastatin 40 and 80 mg; rosuvastatin 10, 20, and 40 mg; ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg; and simvastatin 80 mg), four separate cost-effectiveness models were constructed.

1) The Annual Cost per 1% LDL Decrease model compared the cost-effectiveness of the high % LDL lowering agents on annual cost per 1% LDL decrease using a decision analytical model.
2) The Annual Cost per Patient Treated to Goal model compared the cost-effectiveness of these agents on annual cost per patient successfully treated to NCEP goal using a Monte Carlo simulation model.
3) The Medical Cost Offset Model compared the cost-effectiveness of these agents based on their predicted outcomes and total predicted health care expenditures for CHD and CHD risk-equivalent patients.
4) The Cost per Event-Free Patient model, based on the results of the IDEAL Trial, compared the cost-effectiveness of the agents included in that trial – high-dose (80mg) atorvastatin (Lipitor) vs. low-dose (20-40 mg) simvastatin – using a decision analytic model.

The results of the first three cost-effectiveness analyses showed ezetimibe/simvastatin (Vytorin) to be the most cost effective high % LDL lowering agent. The results of the fourth analysis revealed that high-dose (80 mg) atorvastatin was more effective but considerably more costly compared to low dose (20-40mg) simvastatin. The results of this analysis support use of high dose atorvastatin only in patients who cannot be successfully treated to goal with simvastatin.

For the low to moderate % LDL lowering agents (≤ 45%) in the LIP-1 class (simvastatin 5, 10, 20, and 40 mg, atorvastatin 10 and 20 mg; rosuvastatin 5 mg; ezetimibe/simvastatin 10/10 mg; and all strengths of pravastatin, fluvastatin, fluvastatin extended release lovastatin, lovastatin extended release, niacin/lovastatin, niacin extended release, niacin immediate release, and ezetimibe), the cost-effectiveness of the agents within this subclass was evaluated using the Annual Cost per 1% LDL Decrease model. In pharmacoeconomic terms, lovastatin, lovastatin extended release, simvastatin, and rosuvastatin were located along the cost efficiency frontier and were considered to be the optimal agents. Although these agents differed in terms of cost-effectiveness relative to each other, they were more cost-effective than (dominated) the other agents evaluated.

With respect to atorvastatin/amlodipine, an earlier review did not show additional clinical benefit for amlodipine versus other dihydropyridine CCBs. Single ingredient amlodipine (Norvasc) is non-formulary under the UF. In order to assess the cost effectiveness of atorvastatin/amlodipine, it was compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, based on the weighted average cost per day of therapy. The results of this analysis revealed that atorvastatin/amlodipine was

considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the BIA was to assist the Committee in determining which group of high % LDL lowering LIP-1 agents best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA focused on high % LDL lowering agents because 1) simvastatin could meet the vast majority of the needs of patients requiring low % LDL lowering agents; 2) some low % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin extended release); and 3) of the remaining low % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share. Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included the high % LDL lowering agents atorvastatin and ezetimibe/simvastatin on the UF best achieved this goal when compared to other alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, and 0 absent) to accept the LIP-1 relative cost-effectiveness analysis as presented by the PEC. The P&T Committee concluded that the Uniform Formulary scenario that included atorvastatin, ezetimibe/simvastatin, and simvastatin 80 mg as the high % LDL lowering agents on the UF was the most cost effective UF scenario.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin immediate and extended release, and ezetimibe be maintained as formulary on the UF and that rosuvastatin and atorvastatin/amlodipine be classified as non-formulary under the UF.

C. LIP-1 UF Medical Necessity Criteria

Based on the clinical evaluation of the LIP-1 agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for rosuvastatin:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Treatment with the formulary alternatives has resulted, or is likely to result, in therapeutic failure.
4) The patient previously responded to rosuvastatin and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee noted that some specific situations in which rosuvastatin might be considered medically necessarily were 1) if a patient requires a high % LDL lowering agent in order to meet his or her LDL goal *and* requires a non-CYP3A4-metabolized statin due to potential drug interactions, or 2) if a patient requires a high % LDL lowering agent in order to met his or her LDL goal *and* is not able to reach that goal with any of the formulary high % LDL lowering agents. The P&T Committee also noted that criterion #4 would apply rarely, since changes in statin therapy are unlikely to present a risk of destabilization or serious adverse effects in the vast majority of patients and since rosuvastatin does not offer any significant safety advantages compared to other statins other than not being metabolized through CYP3A4.

Based on the clinical evaluation of the LIP-1 agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criterion for atorvastatin/ amlodipine:

1) Use of formulary alternatives is contraindicated.

The P&T Committee noted that the other conditions for establishing medical necessity provided for in the UF rule do not apply to atorvastatin/amlodipine since the components of this product are available as single ingredients and there is no evidence to support improved efficacy, safety, or tolerability with the combination product vs. its individual components given separately. Amlodipine, a dihydropyridine calcium channel blocker used for hypertension and coronary artery disease, has not been shown to enhance the lipid-lowering effects of atorvastatin. The P&T Committee further noted that since single ingredient amlodipine is non-formulary under the UF, the closest therapeutic alternative to atorvastatin/amlodipine on the UF would be atorvastatin or another UF statin plus a UF dihydropyridine calcium channel blocker [felodipine (Plendil, generics), nifedipine extended release (Adalat CC, Procardia XL, generics), or nisoldipine (Sular)].

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the medical necessity criteria outlined above.

D. LIP-1 Implementation Plan:

Because of contractual considerations associated with the statin drug class affecting MTFs and TMOP, the P&T Committee recommended an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have rosuvastatin or atorvastatin/amlodipine on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for non-formulary LIP-1 agents written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 2 abstained, 0 absent) an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. LIP-1 BCF Review and Recommendations

The P&T Committee had previously determined that one or more low to moderate % LDL lowering agents and no more than one high % LDL lowering agent could be considered for addition to the BCF. Based on the relative clinical effectiveness and cost effectiveness of the agents and taking into account the following considerations, the P&T Committee recommended the following LIP-1 agents for BCF status:

- *Simvastatin* – Simvastatin provides LDL-lowering of up to 40 to 45% at doses ≤ 40 mg/day; can be used to treat 85% of MHS patients who require a statin; has shown proven mortality benefits in primary and secondary prevention trials [HPS; 4S]; is labeled for pediatric use in patients as young as 10 years of age; has an acceptable adverse event profile compared to other statins; and is familiar to MHS providers as evidenced by its current high utilization in the MHS.
- *Pravastatin* – Pravastatin is one of three statins not metabolized via the CYP3A4 system, which is necessary in order to avoid drug interactions in special populations *requiring* treatment with interacting medications (e.g., HIV/AIDS patients, solid organ transplant patients); has shown proven mortality benefits in primary and secondary prevention trials [WOSCOPS, CARE, LIPID]; is labeled for pediatric use in patients as young as 8 years of age; and has the highest utilization in the MHS of the three non-CYP3A4-metabolized statins.
- *Ezetimibe/simvastatin*– The combination of simvastatin and ezetimibe provides additional efficacy for LDL lowering; the 45% to more than 55% LDL lowering attainable with doses higher than 10/20 mg can be used to treat the estimated 15 to 20% of patients who cannot meet goal with simvastatin alone.
- *Niacin extended release* – Niacin is the only agent in the class that has been shown to raise HDL by 25%; has shown proven benefits for mortality, MI, and stroke [Coronary Drug Project]; and has a lower risk for GI adverse events and hepatotoxicity compared to other niacin formulations.

The Committee commented that while atorvastatin is recommended to remain on the UF, MTFs are strongly advised to avoid adding it to local formularies. Simvastatin doses of 20 to 40 mg provide similar efficacy for LDL lowering as atorvastatin but 10 to 20 mg, at a much lower cost due to generic availability. Patient migration from simvastatin to atorvastatin, particularly for patients requiring lower doses, will erode the cost-savings anticipated to occur as generic prices for simvastatin continue to decrease without providing additional clinical benefit. One possible exception to this may be ACS patients, in whom atorvastatin may be preferable based on the results of the PROVE-IT trial (for most patients, this would most likely entail use of 80 mg dose of atorvastatin, based on the lower LDL goals in this patient population).

COMMITTEE ACTION: The P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/simvastatin and niacin extended release as the BCF selections in this drug class.

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZO-DIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on 16 August 2006. The dates of the next meeting are 14-16 November 2006.

_____signed_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	Pending approval	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) - excludes gelcaps and effervescent tablets	Pending approval	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 July 06	27 Sept 06 (60 days)
May 06	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospironone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 July 06	24 Jan 07 (180 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 July 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 July 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

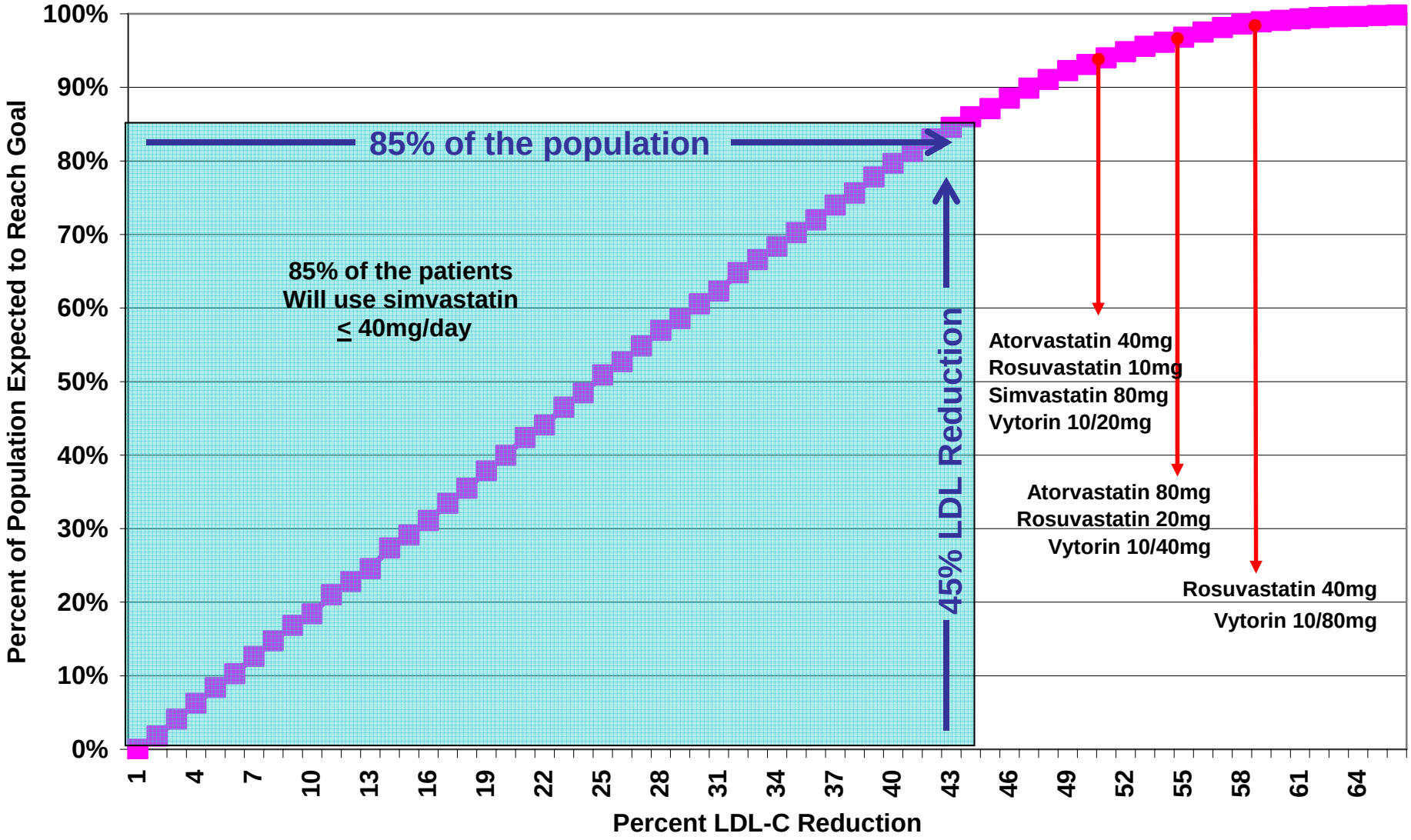
Appendix B – Table 2. Newly Approved Drugs. August 2006 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Dasatinib tabs (Sprycel; BMS) oral multi-kinase inhibitor	Jun 06 ▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib (Gleevec) ▪ Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer medications reviewed. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 20 mg: 180 tabs per 45 days o 50 mg: 180 tabs per 45 days o 70 mg: 90 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 20 mg: 120 tabs per 30 days o 50 mg: 120 tabs per 30 days o 70 mg: 60 tabs per 30 days
Selegiline transdermal system (Emsam; BMS / Somerset) MAO A/B inhibitor	Mar 06 ▪ Acute and longer-term treatment of major depressive disorder in adult patients	No UF recommendation at this meeting. Consideration of UF status deferred until MAO inhibitors reviewed.
Rasagiline tabs (Azilect; Teva) MAO B inhibitor	May 06 ▪ Treatment as monotherapy of early Parkinson's Disease and combination use with levodopa in patients with moderate to advanced stages of Parkinson's Disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's medications reviewed.
Methylphenidate transdermal system (Daytrana; Shire/Noven) amphetamine	Apr 06 ▪ Treatment of attention deficit hyperactive disorder (ADHD) in children 6-12 yrs of age	No UF recommendation at this meeting. Consideration of UF status deferred until ADHD / narcolepsy drug class reviewed in Nov 06.
Lubiprostone caps (Amitiza; Sucampo / Takeda) chloride channel activator	Jan 06 ▪ Treatment of chronic idiopathic constipation in adults	No UF recommendation at this meeting. Consideration of UF status deferred until drug class reviewed.

Appendix C – Table 3. Table of Abbreviations

ACS	acute coronary syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DM	diabetes mellitus
DoD	Department of Defense
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FY	fiscal year
GERD	gastrointestinal reflux disease
GI	gastrointestinal
H2	histamine-2
HDL	high density lipoprotein
HbA1c	glycosylated hemoglobin A1c
IV	intravenous
LDL	low density lipoprotein
MI	myocardial infarction
MHS	Military Health System
MTF	military treatment facility
NSAID	non-steroidal anti-inflammatory drug
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPARs	peroxisome proliferator-activated receptors
PPIs	proton pump inhibitor
QD	once daily
QID	four times daily
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZD	thiazolidinedione
ULN	upper limit of normal
UF	Uniform Formulary

Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction
(NHANES3 Data Modeling by DoD PEC)



Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

<table>
<tr><th rowspan="3">Expected Mean LDL Reduction</th><th colspan="6">Statin</th></tr>
<tr><th>Lovastatin</th><th>Pravastatin</th><th>Simvastatin</th><th>Fluvastatin</th><th>Atorvastatin</th><th>Rosuvastatin</th></tr>
<tr><td>IR - Mevacor, generics
ER - Altoprev</td><td>Pravachol, generics</td><td>Zocor, generics</td><td>IR - Lescol, generics
ER - Lescol XL</td><td>Lipitor</td><td>Crestor</td></tr>
<tr><td>25 to 30%</td><td>20 mg</td><td>20 mg</td><td>10 mg</td><td>40 mg</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>30 to 40%</td><td>40 – 80 mg</td><td>40 mg</td><td>20 mg</td><td>80 mg
(ER only)</td><td>10 mg</td></tr>
<tr><td>40 to 45%</td><td>IR: 80 mg
(40 mg x 2)
ER: 60 mg</td><td>80 mg</td><td>40 mg
or Vytorin 10/10 mg</td><td rowspan="3"></td><td>20 mg</td><td>5 mg</td></tr>
<tr><td>45 to 50%</td><td colspan="2" rowspan="3">Please note: ezetimibe (Zetia) or niacin generally decrease LDL up to an additional 15%</td><td>80 mg
or Vytorin 10/20 mg</td><td>40 mg</td><td>10 mg</td></tr>
<tr><td>50 to 55%</td><td>Vytorin 10/40 mg</td><td>80 mg</td><td>20 mg</td></tr>
<tr><td>>55%</td><td>Vytorin 10/80 mg</td><td colspan="2">40 mg</td></tr>
</table>

IR = immediate release; ER = extended release
Vytorin = ezetimibe/simvastatin

DECISION PAPER:

May 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. **CONVENING**
2. **ATTENDANCE**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a schedule of four weeks on treatment followed by two weeks off treatment. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects, and due to the dosing regimen. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TRICARE Mail Order Pharmacy (TMOP) Program of 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days. (See paragraph 5 on pages 10-11 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant, with a recommended daily maximum of four or fewer units ("lollipops") per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain

should be reevaluated. The Committee agreed that a quantity limit of 120 units per 30 days, 360 units per 90 days should be established for Actiq, based on the daily maximum of four per day recommended in product labeling, in order to address potential concerns of overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion.

***COMMITTEE ACTION*.** The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for oral transmucosal fentanyl citrate (Actiq). (See paragraph 6A on page 11 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Rizatriptan (Maxalt, Maxalt MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days, which is consistent with the maximum recommended dose in product labeling. However, rizatriptan tablets are now available in packages of nine rather than six tablets. The Committee agreed that the 30-day quantity limit for rizatriptan tablets should be increased to 18 tablets, but that the 90-day quantity limit should remain at 36 tablets. This quantity limit would take into account the fact that a substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days, allow for dispensing of whole packages, and avoid increasing the 90-day limit to 54 tablets (3 times 18), which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

***COMMITTEE ACTION*.** The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 6B on pages 11-12 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7. ANTIEMETIC DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) that: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting (RINV), and post-operative nausea and vomiting (PONV); (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for adequate clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring intravenous hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone; (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness , or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that granisetron and ondansetron were the more cost effective 5HT-3 antiemetic drugs; that it is also cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee voted (14 for, 1 opposed, 2 absent, 1 abstained) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF. (See paragraphs 7A and 7B on pages 12-18 P&T Committee minutes)

In addition, the P&T Committee agreed that the current quantity limits for the newer antiemetics should remain unchanged; it also agreed that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed to assist military treatment facilities (MTFs).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of dolasetron (Anzemet) and the conditions for establishing medical necessity for a non-formulary medication provided in the

UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the antiemetics. (See paragraphs 7C on page 18 of the P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P & T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend an effective date no later than the first Wednesday following an implementation period of 60 days. The implementation will begin immediately following the approval of director, TMA. (See paragraph 7D on pages 18-19 of the P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oral and rectal promethazine as the Basic Core Formulary (BCF) agent. (See paragraphs 7E on page 19 of the P&T Committee minutes)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. A total of 36 products were divided into 11 subgroups, based on estrogen content, phasic formulation, and route of administration. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) contraceptives vary in estrogen content, progestin content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices (based on both estrogen and progestogen content), patient response is variable, and there are clinical niches for which multiple choices are required; 6) the alternative formulations (vaginal ring, patch, intramuscular and subcutaneous injection) are required for adequate clinical coverage; 7) none of the reviewed contraceptives are sufficiently less clinically effective than others to be classified as non-formulary based on clinical issues alone.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee agreed (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) all generically available oral contraceptives (OCs) should remain on the UF, because they are generally more cost-effective than brand name contraceptives and non-orally administered contraceptives and because further opportunity exists to negotiate lower prices for generic agents through contracting; 2) all of the non-oral products (Nuvaring, Ortho Evra, Depo Provera and equivalents, Depo-subq Provera 104) should remain on the UF to ensure clinical coverage for patients who need these methods of administration; 3) the brand-only products Yasmin, Yaz, and Ortho Tri-Cyclen Lo should remain on the UF, because they offer clinical and/or economic value; and 4) the brand-only products Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be classified as non-formulary under the UF, because clinically similar alternatives are available at a significantly lower cost. The P&T Committee also agreed (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue on the UF because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception.

In addition, the P&T Committee voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP, with a quantity limit of one Plan B package per co-pay applying to purchased care prescriptions.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) be classified as non-formulary under the UF and that the brand-only products Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically-available products listed in Table 1 (on pages 18-19 of the P&T Committee minutes) be classified as formulary on the UF. The P&T Committee voted (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF. (See paragraphs 8A and 8B on pages 19-30 of P&T Committee minutes)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of the contraceptive agents and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) medical necessity criteria for the contraceptive agents. (See 8C on page 30 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8D on pages 30-31 of P&T Committee minutes for rationale)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following products as the BCF agents.

- EE 20 mcg; 3 mg drospirenone (Yaz)
- EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- EE 30 mcg; 3 mg drospirenone (Yasmin)
- EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
- EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- EE 25 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
- EE 35 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

(See paragraph 8E on pages 31-32 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

APPENDIX A – TABLE 1: Implementation status of UF Decisions

APPENDIX B – TABLE 2: Newly Approved Drugs

APPENDIX C – TABLE 3: Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____
William Winkenwerder, Jr., M.D.
Date: 26 July 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

11 May 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 9 May 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CAPT Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Charlene Reith *for* LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms Julie Liss	DoD Pharmacoeconomic Center
Ms Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms Harsha Mistry	DoD Pharmacoeconomic Center
Ms Elaine Furmaga	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – February 2006 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. February minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the February 2006 DoD P&T Committee on 26 April 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Interim Fluoroquinolone Basic Core Formulary (BCF) Administrative Action: CAPT Buss and CDR Richerson briefed the DoD P&T Committee on the justification and process employed for the 16 March 2006 fluoroquinolone administrative change to the BCF (replacement of gatifloxacin with levofloxacin).

B. Tikosyn Availability in the TRICARE Mail Order Pharmacy (TMOP) Program: Ms. Libby Hearin briefed the DoD P&T Committee that, as of 24 April 2006, Tikosyn is now available through the TMOP. This drug is an anti-arrhythmic which is subject to a controlled distribution program.

C. Beneficiary Advisory Panel (BAP) Briefing: CAPT Buss, CDR Richerson, and CPT Dacus briefed the members of the DoD P&T Committee regarding the 30 March 2006 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

D. Implementation Status of UF Decisions: Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August of 2005. The Committee made the following observations:

- Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.
- Collective utilization of UF agents across all reviewed drug classes and points of service (military treatment facility (MTF), TMOP, TRICARE Retail Pharmacy (TRRx) Network) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 27% reduction in the use of non-formulary agents. Based on all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been an 18% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
- Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).
- For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 81% as projected, but the decrease in the use of non-formulary medications at mail (-2%) and retail (-13%) is significantly less.
- It appears that more beneficiaries are electing to receive non-formulary medications through TMOP. It is unclear at this time whether these beneficiaries are former MTF patients or former TRRx patients.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a period of four weeks followed by two weeks off treatment. Dosage reductions are recommended in 12.5 mg intervals, if needed. There is no 37.5 mg capsule available. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or

drug-related adverse effects, and likelihood of changes to individual dosing regimens. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

One of the new drugs, mecasermin rinfabate (Iplex), is a new version of a medication for which a prior authorization (PA) is already in place. Mecasermin rinfabate was added to the existing PA criteria and forms for mecasermin.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TMOP for 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRRx, the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days.

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant. Based on safety recommendations in product labeling, the daily limit for Actiq is four or fewer units ("lollipops") per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain should be reevaluated. The product is available in multiple strengths—200, 400, 600, 800, 1200, and 1600 mcg—to accommodate individual patient needs and increases in opioid requirements associated with long-term opioid treatment.

The major potential concerns with Actiq are overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion. Actiq is costly; average wholesale price per unit ranges from $17.40 to $51.40 per lollipop, with a federal supply schedule price of $4.89 to $14.56.

The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TMOP and TRRx programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

COMMITTEE ACTION: The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling.

B. RIZATRIPTAN (MAXALT, MAXALT MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days. Based on safety recommendations in product labeling, the safety of treating more than four migraine attacks in a 30-day period has not been established. Doses may be repeated after two hours if the first dose is ineffective, with no more than 30 mg taken in any 24-hour period. Based on this, a quantity limit of 12 tablets per 30 days would allow use up to the recommended maximum, assuming that 10-mg tablets are prescribed. However, rizatriptan packaging has been changed to packages of nine rather than six tablets.

The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend that the quantity unit for rizatriptan tablets and orally disintegrating tablets be increased to 18 tablets per 30 days, 36 tablets per 90 days, based on the following reasoning:

- A substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days.
- The proposed quantity limit allows for dispensing of whole packages of rizatriptan tablets.
- Although the proposed quantity limit does violate the usual rule-of-thumb that 90-day limits will be three times 30-day limits, it is technically feasible to implement and avoids increasing the 90-day to 54 tablets, which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days.

7. ANTIEMETIC DRUG CLASS REVIEW

A. Antiemetic Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, the newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The clinical review included, but was not limited to, the requirements stated in the UF Rule. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

1) Newer Antiemetics

A. Efficacy

Efficacy Measure – The Committee evaluated efficacy of the newer antiemetics in chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV), post-operative nausea and vomiting (PONV) and nausea and vomiting in pregnancy. Complete response was the primary efficacy measure considered. Complete response is a composite outcome of two or more of the following components: no emesis; no nausea; or no need for rescue medication.

When reviewing efficacy trials in nausea and vomiting, direct comparisons of trials is difficult due to large heterogeneity in the trials. Trials conducted in the setting of CINV and RINV are differentiated by the type of chemotherapy administered, emetogenicity potential of the chemotherapy regimen, number of chemotherapy or radiotherapy courses given, and type of malignancy; and show widely varying outcomes. For trials conducted in the setting of PONV, differences in the type of surgical procedure, duration of surgery, and type of anesthesia make direct comparisons difficult.

Chemotherapy-induced nausea and vomiting (CINV)

5-HT3 antagonists – For CINV, there are several head-to-head trials comparing the three 5-HT3 antagonists which overall have shown no differences in efficacy between the intravenous (IV) and oral routes and no consistent differences in efficacy between ondansetron, granisetron and dolasetron. However there is large heterogeneity between the trials.

5-HT3 antagonists – Head-to-head trials and national guidelines: In two head-to-head trials comparing oral 5-HT3 formulations, the complete response rates, as measured by no nausea or emesis or need for rescue therapy, were similar between granisetron and ondansetron (47% vs. 48%), and dolasetron and ondansetron (76% vs. 72%). There were no trials comparing oral dolasetron with oral granisetron, but a trial comparing IV formulations of these two drugs reported no differences in efficacy. Clinical practice guidelines from four national professional groups consider the 5-HT3 antagonists therapeutically interchangeable for CINV.

Aprepitant – The NK-1 receptor antagonist aprepitant is approved for preventing nausea and vomiting associated with highly emetogenic chemotherapy regimens, including high dose cisplatin. Aprepitant has been evaluated in four active-controlled trials in patients undergoing highly emetogenic chemotherapy regimens. When aprepitant was used as adjunctive therapy to 5-HT3 antagonists plus dexamethasone and older antiemetics, a significantly higher percentage of patients achieved complete response rates, vs. placebo.

Radiation-induced nausea and vomiting (RINV)

Systematic Reviews – Systematic reviews state that the evidence shows no consistent differences in efficacy for ondansetron, granisetron and dolasetron for RINV.

Head-to-head trials and national guidelines – There are no head-to-head trials comparing the 5-HT3 antagonists for RINV. One indirect comparison of ondansetron 8 mg and granisetron 2 mg with a historical control group in the prevention of RINV found no differences between the two 5-HT3 antagonists in achieving complete control of emesis (27% with ondansetron vs. 28% with granisetron vs. 0% in the historical control group). There are no published studies evaluating aprepitant for RINV. Clinical practice guidelines from four national professional organizations state that the three 5-HT3 antagonists are therapeutically interchangeable as first-line prophylaxis for RINV.

Post-operative nausea and vomiting (PONV)

Prevention of PON – The majority of studies evaluating prevention of PONV used intravenous (IV) therapies, and rarely continued oral medication after hospital discharge. There are seven head-to-head trials comparing the efficacy of IV formulations of the 5-HT3 antagonists for prevention of PONV; five trials comparing dolasetron with ondansetron, and two trials comparing granisetron with ondansetron. Although the heterogeneity between the trials was large, overall the complete response rates were similar between ondansetron, granisetron and dolasetron. There are no head-to-head trials of oral formulations of the 5-HT3 antagonists for prevention of PONV. A systematic review of four placebo-controlled trials comparing either oral or IV 5-HT3 formulations allowed indirect comparisons between oral dolasetron, IV dolasetron, and IV granisetron. The complete response rates were similar between drugs.

Treatment of PONV – Treatment of PONV most commonly occurs with IV therapy, and is of minor importance to this review. There are no head-to-head trials comparing efficacy of the 5-HT3 antagonists for treatment of PONV. Three systematic reviews of active and placebo controlled trials of the 5-HT3 antagonists in the treatment of PONV provided numbers needed

to treat (NNT) to obtain complete control of further nausea and vomiting (complete response). In one review, no statistically significant differences were found between dolasetron and ondansetron in treating PONV occurring within 6 hours of surgery (NNT of 2.0-3.5 with ondansetron vs. 4.2-6.1 with dolasetron). In the same review there were no significant differences between granisetron and ondansetron in treating PONV occurring < 24 hours after surgery (NNT of 3.3-6.3 with ondansetron vs. 2.4-3.3 with granisetron). The NNTs from all three reviews were similar for ondansetron, granisetron, and dolasetron. There are no published studies evaluating aprepitant for PONV.

Nausea and vomiting in pregnancy

Systematic reviews and MHS utilization – No newer antiemetics are FDA-approved for treating nausea and vomiting in pregnancy. An evidenced-based review concluded that there is insufficient data to recommend use of ondansetron as a first-line agent for this indication. A database linking prescription data with diagnosis codes shows that 21% ondansetron usage in the MHS is for nausea and vomiting in pregnancy.

Clinical trials and case reports – One trial compared IV ondansetron 10 mg with IV promethazine 50 mg in 30 women hospitalized with hyperemesis gravidarum. No differences were found in any outcome measure. One published case report showed that ondansetron 8 mg IV given twice daily was effective at reducing emesis, and that ondansetron 4 mg orally given three times daily for 25 weeks was also effective.

National guidelines – Guidelines from the American College of Obstetricians and Gynecologists (ACOG) state that ondansetron may be used IV as third line therapy if dehydration is present, and IV fluid replacement and dimenhydrinate, metoclopramide, or promethazine have failed to control symptoms. The 5-HT3 antagonists and aprepitant are rated as pregnancy category B by the FDA.

B) Safety / Tolerability

Major adverse events – Ondansetron, granisetron and dolasetron all carry a class warning regarding potential prolongation of the QTc interval. The risk is dose dependent. All three 5-HT3 antagonists can rarely cause anaphylaxis; ondansetron and granisetron can rarely cause bronchospasm. Aprepitant has rarely been associated with Stevens-Johnson Syndrome and angioedema.

Minor Adverse events – For the newer antiemetics, the most commonly reported adverse effect is headache, occurring in 8-18% of patients. Asthenia/fatigue, constipation, and increases in liver enzymes also occur with an incidence of greater than 5%. Aprepitant is associated with diarrhea, dizziness, hiccups and increases in liver enzymes, all occurring in <6% of patients. No dosage adjustments are necessary for the four newer antiemetics in patients with renal dysfunction. The maximal dose of ondansetron should be limited to 8 mg in patients with severe hepatic dysfunction.

Drug Interactions – All three 5-HT3 antagonists are metabolized by varying degrees through the Cytochrome P450 (CYP450) enzyme system. The 5-HT3 antagonists are metabolized by multiple pathways within the system. Ondansetron is metabolized to the greatest extent, followed by dolasetron and granisetron; however, there are no requirements for ondansetron dosage adjustments when given with CYP450 inducers. Aprepitant can inhibit Cytochrome P450 3A4 (CYP3A4) enzymes, and is associated with the most clinically important drug interactions of the newer antiemetics. Aprepitant increases concentrations of dexamethasone up

to two and half times, and if administered concomitantly with dexamethasone, the dexamethasone dose should be reduced by 50%.

C) Other Factors

Available formulations – Ondansetron is available in several oral formulations, including an oral tablet, oral solution, and orally dissolving tablet (ODT). Ondansetron ODT may be swallowed without the need to consume additional liquid that could trigger vomiting; however, it should be used with caution in patients with phenylketonuria, as it contains aspartame. Granisetron is available in an oral tablet and oral solution.

Pediatrics – Ondansetron and dolasetron are approved for prevention of CINV in pediatrics. Ondansetron is approved for use in children as young as four years of age, while dolasetron is approved for use in children as young as two years. The oral formulation of granisetron is not approved for use in children; however the IV formulation is approved for use in children older than two years. Aprepitant is not approved for use in the pediatric population.

*FDA indicatio*ns – Of the newer antiemetics, ondansetron has the most FDA-approvals (CINV, RINV, and PONV). Granisetron is approved for CINV and RINV, and dolasetron is approved for CINV and PONV. Aprepitant is approved for prevention of CINV caused by moderately or highly emetogenic chemotherapy regimens.

Quantity Limits – There are existing quantity limits in place for the four newer antiemetics, which take into account FDA-approved indications and dosing recommendations for CINV, RINV, and PONV. Quantity limits may be overridden for individual patients if greater quantities are determined to be medically necessary. A frequent reason for medical necessity is severe nausea and vomiting associated with pregnancy (i.e., hyperemesis gravidarum).

MHS Utilization – The most widely prescribed newer antiemetic in the MHS is ondansetron, with 3,500 prescriptions per month. Over 51% of the MHS usage of the newer antiemetics is for CINV; nausea and vomiting in pregnancy accounts for 15% of the usage of the newer antiemetics, RINV comprises 10% of usage, PONV 2% of usage, and other diagnoses 22% of usage.

Provider Survey – Overall, providers preferred ondansetron, primarily due to more familiarity over the other 5-HT3 antagonists. Several providers commented that they preferred the newer antiemetics over the older antiemetics due to less sedation, which is particularly beneficial for active duty members or those with childcare responsibilities.

Conclusion for the newer antiemetics – The committee concluded that there is insufficient evidence to suggest that the antiemetic effects of the 5-HT3 antagonists differ significantly between drugs. Ondansetron, granisetron and dolasetron show efficacy for CINV, RINV, and PONV. Ondansetron shows efficacy for treating nausea and vomiting in pregnancy, but should be used third line. Aprepitant has shown efficacy in placebo controlled trials for CINV when used as an adjunct to 5-HT3 antagonists for patients undergoing highly emetogenic chemotherapy regimens. The adverse effect profiles of 5-HT3 antagonists and aprepitant are similar in nature. Ondansetron has the largest number of oral formulations, and is approved for use in pediatrics, along with dolasetron.

2) Older Antiemetics

A) Place in therapy and national guidelines – The older antiemetics are still widely used to treat nausea, vomiting and motion sickness. Many of the older antiemetics are mentioned in national guidelines for the treatment of CINV and PONV, and are commonly used in these

settings. Prochlorperazine is used for indications other than nausea and vomiting, including for anxiety and schizophrenia. Promethazine is a second-line therapy for treatment of nausea and vomiting in pregnancy, according to ACOG guidelines. Dronabinol is commonly employed in the treatment of glaucoma, AIDS, chemotherapy-related anorexia and spasticity associated with multiple sclerosis.

B) Adverse effects – All the older antiemetics are associated with drowsiness, dizziness and somnolence. The phenothiazines (prochlorperazine, thiethylperazine) and antihistamines (meclizine, promethazine) can cause rare but serious adverse events including neuroleptic malignant syndrome, reversible dystonic reactions, seizures, irreversible tardive dyskinesias, agranulocytosis and severe leukopenia. Common adverse effects of the anticholinergic agents (trimethobenzamide, scopolamine) include dry mouth and eyes, and urinary retention in elderly patients. Confusion, distorted perception, and rare hallucinations and severe paranoia have been linked to dronabinol.

C) Other factors – Four of the older antiemetics are available in generic formulations; meclizine, promethazine, prochlorperazine, and trimethobenzamide. The older antiemetics are available in various dosage forms that are advantageous for use as rescue therapy in nausea and vomiting when the oral route can not be used. Prochlorperazine, promethazine and trimethobenzamide are available in suppository form. Transdermal scopolamine patches offer a topical route, but should not be used for acute nausea and vomiting, due to delayed absorption. With the exception of meclizine, which has a pregnancy category B rating, all of the older agents are ranked pregnancy category C by the FDA. The older antiemetics are indicated for use in children, with the exception of thiethylperazine. The package insert for promethazine has a black box warning regarding use in children under the age of two due to respiratory depression. Dronabinol is a Drug Enforcement Administration (DEA) controlled schedule III substance. The most widely prescribed older antiemetic in the MHS is promethazine, with 40,000 prescriptions per month.

*Conclusions for the older antiemetic*s – The older antiemetics are frequently used for nausea and vomiting, and several are used for indications other than emesis. The availability of non-oral dosage formulations is useful for rescue therapy of nausea and vomiting. Thiethylperazine is the only older antiemetic not approved for pediatric use, although promethazine should be used with caution in children due to possible respiratory depression. All the older agents can cause sedation and dizziness.

Overall clinical effectiveness conclusion – The Committee concluded: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with CINV, RINV, and PONV; (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring IV hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics is sufficiently less clinically effective than the others to be classified as non-formulary, based on clinical issues

alone; and (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness, or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. Antiemetic Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Three separate pharmacoeconomic analyses were performed: a cost-minimization analysis (CMA) on the newer 5-HT3 antiemetics subclass, followed by a budget impact analysis (BIA); a cost-effectiveness analysis (CEA) of aprepitant to evaluate its place in therapy; and lastly a cost-analysis on the older antiemetic subclass.

Given the evidenced-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the 5-HT3 antagonists differed in regards to efficacy, safety, tolerability, and clinical outcomes in the treatment of CINV, RINV, and PONV, a CMAwas performed to determine the relative cost-effectiveness of the agents within the 5-HT3 subclass. The cost examined was the total weighted average cost per treatment episode across all points of service. Results of the analysis for the newer antiemetic drugs (5HT-3s) showed granisetron was the most cost effective 5HT-3 antiemetic agent with the lowest average cost per treatment episode across the MHS.

The results of the above analysis were then incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of 5-HT3 antagonists best meet the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the results of the BIA and other clinical and cost considerations (ondansetron is projected to undergo generic competition in 2006), the Committee agreed that a group of 5-HT3 antagonists that included granisetron and ondansetron best achieved this goal when compared to other combination groups of 5-HT3 antagonists, and thus were determined to be more cost-effective relative to other combination groups.

A CEA was also conducted to evaluate the place in therapy for aprepitant, a NK-1 antagonist. Aprepitant is indicated for adjunctive therapy along with other antiemetics for delayed nausea and vomiting associated with chemotherapy. The results of the CEA showed that: 1) the blanket purchase agreement (BPA) offered price for aprepitant improved its cost-effectiveness over baseline, and 2) when total health care costs are considered, aprepitant is cost-effective as an adjunct in the treatment of chemotherapy induced nausea and vomiting.

Finally, a cost analysis for the older antiemetics (promethazine, prochlorperazine, trimethobenzamide, thiethylperazine, meclizine, scopolamine, and dronabinol) was presented. The results of the cost-analysis showed that the cost associated with these agents is about 25% of the overall anti-emetic drug spend. However, 72% of the costs for these older anti-emetic

drugs were generated in the retail setting. Over half of this figure was for promethazine, which is available in generic form. The conclusion of the cost analysis was that no savings would be achieved by placing any of the older antiemetics in the non-formulary tier of the UF.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the antiemetic pharmacoeconomic analyses presented by the PEC. The Committee concluded that granisetron and ondansetron are the more cost effective 5HT-3 antiemetic drugs; that dolasetron is not cost-effective relative to the other 5-HT3 antagonists, that it is cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

The P&T Committee also recommended that the current quantity limits for the newer antiemetics should remain unchanged. They agreed, however, that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed. Such criteria would be particularly beneficial for MTFs.

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF.

C. Antiemetic Medical Necessity Criteria: Based on the clinical evaluation of the antiemetics, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for dolasetron.

1) Use of formulary antiemetics is contraindicated, and dolasetron is not contraindicated.
2) The patient has experienced significant adverse effects from the formulary antiemetics, or is likely to experience significant adverse effects from formulary antiemetics, and the patient is expected to tolerate dolasetron.
3) Treatment with formulary antiemetics has resulted in therapeutic failure, and the patient is expected to respond to dolasetron.

Because of the clinical differences between antiemetics, the Committee agreed that the most appropriate formulary alternatives for dolasetron are the other 5-HT3 antagonists.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the anti-emetic medical necessity criteria.

D. Antiemetic UF Implementation Period: The P&T Committee recommended an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have dolasetron on their local formularies. MTFs will be able to fill non-formulary requests for dolasetron only if both of the following conditions are met: 1) the prescription is written by an MTF provider, and 2) medical necessity is established. MTFs

may (but are not required to) fill a prescription for dolasetron written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) for an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

E. Antiemetics BCF Review and Recommendations: The P&T Committee had previously determined that zero to one newer antiemetics and at least one older antiemetic should be added to the BCF, based on clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that promethazine be maintained on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to maintain oral and rectal promethazine on the BCF.

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

A. Contraceptive Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. Contraceptive products were divided into the subgroups outlined in Table 1, based on estrogen content, phasic formulation, and route of administration.

Table 1: Oral, Transdermal Patch, Vaginal Ring, and Injectable Contraceptive Products Available in the U.S.
(Source of Prescription Data: Pharmacy Data Transaction Service)

Subgroup	**Generic Product Description** (Ethinyl estradiol = EE; progestogen)	**Brand Name**	**Manufacturer**	**Total MHS Rxs** Jan-Dec 05
Monophasic OCs with 20 mcg EE	EE 20 mcg; 0.1 mg levonorgestrel	Alesse	Wyeth	86,569
		Aviane	Duramed	
		Lutera	Watson	
		Lessina	Barr	
		Levlite	Berlex	
	EE 20 mcg; 1.0 mg norethindrone	Junel 1/20	Barr	2,038
		Loestrin-21 1/20	Warner Chilcott	
		Microgestin 1/20	Watson	
	EE 20 mcg; 1.0 mg norethindrone; ferrous fumarate	Junel Fe 1/20	Barr	18,356
		Loestrin Fe 1/20	Warner Chilcott	
		Microgestin Fe 1/20	Watson	
	EE 20 mcg; 3 mg drospirenone	Yaz	Berlex	Approved March 2006
Monophasic OCs with 30 mcg EE	EE 30 mcg; 0.15 mg levonorgestrel	Levlen 28	Berlex	25,092
		Levora 0.15/30-28	Watson	
		Nordette-28	Duramed/Barr	
		Portia-28	Barr	
	EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	Duramed/Barr	20,153
	EE 30 mcg; 0.3 mg norgestrel	Cryselle	Barr	123,501
		Lo/Ovral	Wyeth	
		Low-Ogestrel	Watson	
	EE 30 mcg; 0.15 mg desogestrel	Apri	Barr	59,086
		Desogen	Organon	
		Ortho-Cept	Ortho	
		Reclipsen	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
		Solia	Prasco	
	EE 30 mcg; 1.5 mg norethindrone acetate	Junel 1.5/30	Barr	1,048
		Loestrin 1.5/30	Duramed/Barr	
		Microgestin 1.5/30	Watson	
	EE 30 mcg; 1.5 mg norethindrone; ferrous fumarate	Junel Fe 1/5/30	Barr	19,472
		Loestrin-FE 1.5/30	Duramed/Barr	
		Microgestin Fe 1.5/30	Watson	
	EE 30 mcg; 3 mg drospirenone	Yasmin	Berlex	125,965
Monophasic OCs with 35 mcg EE	EE 35 mcg; 0.5 mg norethindrone	Brevicon	Watson	144
		Modicon	Ortho	628
		Necon	Watson	
		Nortrel 0.5/35	Barr	
	EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	Warner-Chilcott	6,681
		Ovcon-35 chewable		
	EE 35 mcg; 0.25 mg norgestimate	Mononessa	Watson	46,123
		Ortho-Cyclen	Ortho	
		Previfem	Teva	
		Sprintec	Barr	
	EE 35 mcg; 1.0 mg norethindrone	Necon	Watson	92,114
		Norinyl 1+35	Watson	
		Nortrel	Barr	
		Ortho-Novum 1/35	Ortho	
	EE 35 mcg; 1.0 mg ethynodiol diacetate	Demulen 1/35	Pharmacia/Upjohn	17,171
		Kelnor	Barr	
		Zovia 1/35E	Watson	
Monophasic OCs with 50 mcg EE or mestranol	Mestranol 50 mcg; 1 mg norethindrone	Necon	Watson	3,979
		Norinyl 1+50	Watson	
		Ortho-Novum 1/50	Ortho	
	EE 50 mcg; 1 mg norethindrone	Ovcon-50	Warner Chilcott	2,061
	EE 50 mcg; 1 mg ethynodiol diacetate	Demulen 1/50	Pharmacia/Upjohn	1,368
		Zovia 1/50E	Watson	
	EE 50 mcg; 0.5 mg norgestrel	Ogestrel	Watson	2,938
		Ovral-28	Wyeth	
Biphasic OCPs	EE 35 mcg; 0.5/1.0 mg norethindrone	Necon	Watson	168
		Ortho-Novum 10/11	Ortho	
	EE 20/10 mcg; 0.15 mg desogestrel	Kariva	Barr	22,731
		Mircette	Duramed/Barr	
Triphasic OCPs	EE 25 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen Lo	Ortho	101,349
	EE 35 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen	Ortho	331,429
		Trinessa	Watson	
		Tri-Previfem	Teva	
		Tri-Sprintec	Barr	
	EE 30/40/30 mcg; 0.05/0.075/0.125 mg levonorgestrel	Enpresse	Barr	76,559
		Tri-levlen	Berlex	
		Triphasil	Wyeth	
		Trivora	Watson	
	EE 35 mcg; 0.5/1/0.5 mg norethindrone	Aranelle	Barr	1,516
		Leena	Watson	
		Tri-Norinyl	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
	EE 35 mcg; 0.5/0.75/1 mg norethindrone	Necon 7/7/7	Watson	59,536
		Nortrel 7/7/7	Barr	
		Ortho-Novum 7/7/7	Ortho	
	EE 25 mcg; 0.1/0.125/0.15 mg desogestrel	Cesia	Prasco	5,648
		Cyclessa	Organon	
		Velivet	Barr	
	EE 20/30/35 mcg; 1.0 mg norethindrone	Estrostep Fe	Warner-Chilcott	9,916
Progestogen-Only OCPs	0.35 mg norethindrone	Errin	Barr	71,003
		Ortho Micronor	Ortho	
		Jolivette	Watson	
		Camila	Barr	
		Nora-BE	Watson	
		Nor-QD	Watson	
Contraceptive patch	EE/Norelgestromin ~ 60% higher exposure than oral contraceptive with 35 mcg EE (= >50 mcg EE), but lower peak concentrations	Ortho Evra	Ortho	268,223
Contraceptive vaginal ring	Daily dose: ~ EE 15 mcg; ~0.12 mg etonogestrel	Nuvaring	Organon	55,415
Injectable Contraceptives	104 mg/ 0.65mL depot medroxyprogesterone acetate	Depo-subqProvera104	Pfizer	39
	150 mg/mL depot medroxyprogesterone acetate	Depo-provera (disp syr)	Pharmacia/Upjohn	10,912
		Medroxyprogesterone acetate (disp syr)	Sicor	
		Depo-provera (vial)	Pharmacia/Upjohn	59,931
		Medroxyprogesterone acetate (vial)	Greenstone	
			Sicor	
Emergency Contraceptives	0.75 mg levonorgestrel	Plan B	Duramed/Barr	4,049

Oral contraceptives (OCs) differ from most other drug classes in two regards: 1) unique combinations of varying strengths of specific estrogen and progestogen components are considered to be separate products (e.g., Ortho-Novum 1/35 and Ortho-Novum 1/50) rather than different strengths of the same product; and 2) generic versions of branded contraceptive products typically have brand names of their own. Other factors (such as FDA-approved special packaging/labeling or the content of "placebo" tablets) may also affect generic equivalency. For the purpose of making formulary recommendations, the P&T Committee made its selections at the "generic product" level as outlined in Table 1, consistent with its actions in other drug classes. For example, ethinyl estradiol 35 mcg; 1.0 mg norethindrone constituted a single line item to be considered for placement on the UF. Specific originator products (e.g., Ortho-Novum 1/35) and generic equivalents (Necon, Norinyl, and Nortrel) were not considered individually.

The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve-month period ending 31 Jan 2006, 552,272 MHS beneficiaries received one or more contraceptive prescriptions, accounting for about $80 million in annual expenditures across the MHS.

1) DoD Provider Input

A total of 79 survey responses were received from providers in time to be tabulated for P&T Committee review. Responders were family practice physicians (26), women's health nurse practitioners (21), obstetricians /gynecologists (18), family nurse practitioners (6), certified nurse-midwives (4), or other providers (4). A number of responses, including some from internal medicine physicians, were received too late for tabulation, but were not qualitatively different from other providers' responses.

2) Potential Differences between Contraceptive Products

There are a wide variety of contraceptive products. Points of difference include estrogen content; progestogen content; regimen (e.g., extended use, 24-day cycle products); phasic formulation; proven or potential usefulness for other conditions in addition to contraception (e.g., acne); and route of administration. Most OCs contain both an estrogen and a progestogen component. Progestogen-only OCs are used much less commonly than combined OCs, but fill a distinct clinical niche for women who should not receive estrogen.

Estrogen content – The estrogen component in almost all combined contraceptives is ethinyl estradiol; mestranol (a prodrug of ethinyl estradiol) is used in a few older products. The amount of ethinyl estradiol included in specific products varies from as little as 15-20 mcg per day to as much as 50 mcg per day in older products. Low-estrogen products (20-30 mcg of ethinyl estradiol) are most commonly used. The availability of a wide array of contraceptive products with differing ethinyl estradiol levels is necessary because of the need to maintain contraceptive effectiveness and control irregular bleeding (cycle control) while minimizing common adverse effects and thromboembolic risk. Considerable intra- and inter-patient variability in estrogen metabolism contributes to the need for multiple products. Another contributing factor may be the fact that adverse effects and cycle control problems with all contraceptive products tend to occur more frequently in the first few cycles after initiation of treatment; switching products prematurely may lead women to falsely believe that they cannot tolerate specific products.

Progestogen content – Contraceptive products available in the U.S. include a variety of progestogens. Based on chemical structure, a recent Cochrane review (Maitra et al, 2005) classified progestogens (not including non-U.S. products) as follows:

- First generation: norethindrone, ethynodiol diacetate
- Second generation: levonorgestrel, norgestrel
- Third generation: desogestrel, norgestimate (some authors classify norgestimate as second generation, since it is partially metabolized to levonorgestrel)
- Unclassified: drospirenone

The injectable contraceptives (Depo-Provera and generics, Depo-subq Provera 104) contain depot medroxyprogesterone acetate (DMPA), a derivative of progesterone.

Regimen – While most combined contraceptives—including the transdermal patch and vaginal ring—are based on a 21-day "on", 7-day "off" cycle, this regimen is often modified in clinical practice by either extending the active treatment period and/or shortening the medication-free period. Extended treatment cycles or continuous (daily) use of combined OCs have been used

clinically for many years to treat menstrual migraines, dysmenorrhea, endometriosis, and other conditions associated with menses. Over time, extended or continuous use of OCs for practical or convenience reasons (reducing or eliminating menstrual periods) has come into more common use. A Cochrane review [Edelman et al, 2005] concluded that extended or continuous use of contraceptives was reasonable for women without contraindications, based on the results of six trials. A single contraceptive product, Seasonale, is labeled and specially packaged for extended cycle use (84 days on, 7 days off), although any monophasic OC could be used for extended or continuous treatment by eliminating unneeded placebo tablets.

A majority of DoD providers surveyed indicated that extended or continuous cycle offered advantages over conventional dosing, with 29 citing convenience/lifestyle advantages, and 36 citing advantages in treating menstrual-related problems. A total of 43 providers (out of 62 commenting) did not agree that Seasonale provided a benefit relative to another OC given on the same dosing schedule (84 days on, 7 days off); 19 commented on the greater convenience of packaging. Many providers without experience with Seasonale reported using other OCs on an extended-cycle basis.

Two newly approved low-estrogen contraceptive products, Loestrin 24 Fe and Yaz, are labeled for use as a 24-day on, 4-day off regimen. The shortened "off" cycle is intended to decrease adverse effects associated with hormone withdrawal. It may also provide a greater safety margin for contraceptive effectiveness by decreasing the likelihood of follicle development during the "off" cycle.

Phasic formulations – Biphasic and triphasic oral contraceptives attempt to "mimic" changes in levels of estrogen and progesterone seen during the normal menstrual cycle, in an attempt to decrease adverse effects by decreasing hormonal steroid exposure. The introduction of these products was probably primarily a reaction to the controversy about the relationship between thromboembolic events and progestogen content, since lower total amounts of progestogens can be achieved by providing a varying amount throughout the cycle. The biphasic OCs initially introduced to the market were rapidly superseded by triphasic OCs, resulting in infrequent use of the older biphasic products. Triphasic products, which vary doses of progestogen and/or estrogen three times during the treatment period, remain popular.

Although classified as a biphasic product, Mircette and its generic equivalents (21 days of EE 20 mcg/desogestrel 150 mcg followed by 2 days of placebo and 5 days of 10 mcg EE) are more similar to a low-estrogen monophasic product plus supplemental estrogen than to the older biphasic products. Mircette may be useful in perimenopausal women due to the more constant estrogen levels.

Usefulness for other conditions – Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, reduction of acne and dysmenorrhea, and favorable effects on other conditions, such as endometriosis pain and menstrual migraines. Relatively few contraceptive products have FDA-approved indications in addition to prevention of pregnancy. However, given the lack of substantial differences between products with regard to contraceptive effectiveness, the choice of a specific contraceptive product may depend on its proven or potential usefulness for another condition.

Alternative routes of administration – Contraceptive products offering alternative routes of administration include DMPA injections, a transdermal patch (Ortho Evra), and a vaginal ring (Nuvaring). Two DMPA formulations are available: 150 mcg, given by deep intramuscular (IM) injection (Depo-Provera, generics), and 104 mcg (Depo-subq Provera 104), given by

subcutaneous (SC) injection (less painful and may allow patient self-administration). DMPA injections are given every 11 to 13 weeks. In addition to prevention of pregnancy, the 104 mcg formulation is also approved by the FDA for endometriosis pain. The transdermal patch is applied weekly for three weeks, followed by a patch-free week, while the vaginal ring is inserted on a monthly basis and then removed after 3 weeks, followed by a 7-day ring-free period.

Emergency contraception – The only product currently labeled as emergency contraception is levonorgestrel 0.75 mg (Plan B), which is given as one dose (1 tablet) within 72 hours after unprotected intercourse and a second dose 12 hours later. A combination emergency contraception product (Preven) was discontinued in 2004. In addition to Plan B, the FDA has declared several brands of combined OCs to be safe and effective for emergency contraception, including Ovral, Alesse, Nordette or Levlen, Lo/Ovral, Triphasil or Tri-Levlen. Progestogen-only regimens such as Plan B have been shown to be more effective and better tolerated for emergency contraception than combination OCs.

3) Efficacy / Effectiveness

Contraceptive effectiveness – All of the reviewed contraceptives are highly effective at preventing pregnancy when used correctly. Progestogen-only OCs may be slightly less effective than combined OCs and for that reason have stricter use requirements (i.e., they must be taken at the same time each day, without an "off" period). There is some question as to whether the lowering of estrogen content in combined OCs over time has resulted in a decrease in contraceptive effectiveness, although data are lacking. Methods that reduce the potential for user error (e.g., injectable contraceptives) are known to decrease "actual use" failure rates. Whether or not potentially improved compliance related to less-frequent dosing of the transdermal patch and vaginal ring results in decreases in "actual use" failure rates remains to be seen; contraceptive effectiveness so far appears similar to combined OCs. Drug interactions and patient weight may also affect contraceptive effectiveness.

Overall, the differences in contraceptive effectiveness among the reviewed contraceptive products appear minor, with no reliable evidence to suggest substantial differences in contraceptive effectiveness based on progestogen content, phasic formulation, or regimen.

Efficacy in treating other conditions

Acne – All combined contraceptives are likely to have beneficial effects on acne, based on several potential mechanisms, including decreased production and increased binding of free testosterone, blocking androgen receptors, and inhibiting conversion of testosterone to dihydrotestosterone in the hair follicles and skin. Clinically, progestogens with relatively low binding to androgen receptors have been preferred for patients with androgenic adverse effects (such as acne or hirsutism), although actual differences between products are unclear. A 2005 Cochrane review [Arowojolu et al] reviewed 14 head-to-head contraceptive trials (9 different comparisons) focusing on acne; unfortunately, most products included in the review are not currently available in the U.S. The three trials remaining either reported no difference between products or inconclusive results.

Contraceptive products with an additional FDA approved indication for acne include Ortho Tri-Cyclen (a triphasic product containing 35 mcg EE and varying amounts of norgestimate, which is now generically available) and Estrostep Fe (a triphasic product containing varying amounts of estrogen and 1 mg norethindrone). Trials with products containing drosperinone, which has anti-androgen properties, have reported comparable to somewhat superior results

compared to a product containing cyproterone (a progestogen traditionally favored in the United Kingdom for acne treatment, but not available in the U.S.) [Van Vloten et al, 2002] and Ortho Tri-Cyclen [Thorneycroft et al, 2004].

The vast majority of DoD providers surveyed (76/79) agree that other OCs work as well for acne as Ortho Tri-Cyclen, despite its FDA indication.

Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD) – Continuous use of OCs may decrease premenstrual symptoms. Several clinical trials with drospirenone-containing OCs have reported favorable effects on PMDD, a severe form of PMS, especially with regard to fluid retention and weight fluctuations ("bloating").

Endometriosis pain – OCs with higher progestational activity and/or continuous use of contraceptives may be preferred in patients with endometriosis pain, which is related to the menstrual cycle. Progestogen-only DMPA injections are associated with improvements in endometriosis; the subcutaneous administered 104 mg strength (Depo-subq Provera 104) has an FDA-approved indication for endometriosis pain.

Heavy menstrual bleeding and dysmenorrhea (menstrual pain) – Combined OCs have been used to treat dysmenorrhea (by decreasing prostaglandins and thus uterine motility/cramping) and heavy menstrual bleeding (by promoting regular shedding of a thinner endometrial lining) since their introduction in 1960. While clinical evidence supports efficacy, most of the literature addresses the older products (≥ 50 mcg EE) and does not support conclusions about the efficacy or comparative efficacy of currently used low estrogen products.

4) Safety and Tolerability

Serious adverse events/contraindications – Use of combined OCs is associated with increased risk of several serious conditions, including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the absolute risk of these events is very low in women without additional risk factors. Much of the available epidemiological data was obtained from studies using higher estrogen and progestogen doses than those currently in use; the effect of long-term, low-estrogen OC use has yet to be determined. Risks associated with the patch and vaginal ring are largely unknown, although they are presumed to be similar to those of combined OCs.

Use of combined OCs is associated with an increased risk of venous thromboembolism (VTE) (e.g., deep vein thrombosis, pulmonary embolism). Most data relate to products with higher doses of estrogen than are currently used; low estrogen products may be associated with a lower risk. The issue of whether third-generation progestogens (e.g., desogestrel) are associated with an increased thromboembolic risk compared to second-generation progestogens has been controversial; however, many sources now appear to agree that there is a modestly increased risk with products containing desogestrel, compared to those containing levonorgestrel. The risk of VTE with norgestimate appears similar to levonorgestrel and lower than desogestrel, based on limited data [Gomes et al, 2004]. Epidemiological data for drospirenone is not yet available. A 2004 safety review reporting 3-year interim results from a large, controlled, postmarketing surveillance study [Heinemann & Dinger, 2004] did not suggest an excess risk with drospirenone-containing products compared to those containing levonorgestrel or other progestogens.

An increased risk of myocardial infarction (MI) and stroke has been associated with OC use, primarily in smokers or women with underlying risk factors for coronary artery disease. Most data relate to products with higher doses of estrogen than are currently used; low estrogen

products may be associated with lower risk. Whether progestogen content affects the risk of MI or stroke is unclear.

Absolute contraindications to the use of combined contraceptives include: previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, or valvular heart disease with complications; severe hypertension; headaches with focal neurologic symptoms; known or suspected estrogen-dependent tumor (e.g., endometrial, breast cancer); liver disease; cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use; major surgery with prolonged immobilization; pregnancy; undiagnosed abnormal uterine bleeding; and women over age 35 years who smoke.

Common adverse effects – In general, adverse effects of oral, transdermal, or vaginal ring contraceptives may include: breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.

Estrogen content and adverse effects – Logically, lower estrogen products (e.g., ≤ 20 mcg EE) are associated with a lower risk of estrogen-related adverse effects and a lower risk of thromboembolic events (although data are limited). However, this must be balanced against a greater vulnerability to compromises in contraceptive effectiveness due to missed doses or drug interactions, a potential decrease in non-contraceptive benefits (e.g., reduction in risk of ovarian cancer or protection against functional ovarian cysts), and a higher incidence of cycle control problems (e.g., breakthrough bleeding and spotting). Determination of the "best" estrogen dose – reliable pregnancy prevention with acceptable cycle control and minimal adverse effects – is complicated by wide inter-patient variability in hormonal blood levels.

Progestogen content and adverse effects – There is considerable difference of opinion among providers concerning the extent to which the choice of progestogen affects tolerability. Products containing third-generation progestogens appear to have fewer androgenic effects than the first- and second-generation products, and may be favored in patients with androgenic adverse effects such as acne or hirsutism (although all combined OCs reduce free testosterone levels and therefore tend to have favorable effects on acne). According to a Cochrane review last updated in 2005 (Maitra et al), second- and third-generation products may offer some advantage over first generation products with respect to cycle control (e.g., minimizing spotting or breakthrough bleeding). The magnitude of the difference is unclear.

Drospirenone is a derivative of spironolactone with anti-mineralocorticoid and anti-androgenic properties similar to progesterone. In addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney; the effect is similar to 25 mg of spironolactone. As a consequence, drospirenone reduces fluid retention and weight fluctuations ("bloating"). It may cause concerns about hyperkalemia in patients with a predisposing condition or on other medications that increase potassium levels (women receiving daily, long-term treatment with medications that can increase potassium should have their serum potassium levels checked during the first treatment cycle). While precautions are indicated, there appears to be little evidence to cause serious concern. About 14 million women worldwide have received drospirenone-containing products, according to the manufacturer.

Adverse effects with the transdermal patch – Based on a comparative trial, adverse effects of the transdermal patch appear similar to a combined OC comparator, with the exception of a higher incidence of site reactions, breast symptoms (e.g., breast tenderness), and dysmenorrhea. Another obvious concern with the patch is adhesion; about 5% of patches used during clinical trials had to be replaced, because they fell off or partially detached. A small study cited in

labeling showed a relatively small percentage of patches falling off under conditions of heat, humidity, or exercise; anecdotal reports and survey results from deployment sites suggest a much larger percentage. Site reactions, reported in about 17% of patients, were mostly mild to moderate (92%). Skin pigmentation changes were rarely reported (overall in <1% of patients), with one severe case reported in labeling.

Based on pooled data from North American pivotal trials (Archer et al, 2002), the patch may have compliance advantages compared to combined OCs, with perfect compliance (21 days of drug-taking followed by 7 drug-free days) in 79% of cycles for patients receiving comparator OCs vs. 98% receiving the patch.

DoD providers surveyed cited advantages of the transdermal patch as being improved compliance with infrequent dosing and availability of a different dosing option; disadvantages included the patch coming off, the uncertainty regarding estrogen exposure and VTE risk, the incidence of skin reactions, and weight limitations.

A recent pharmacokinetic study noted that systemic exposure (area under the curve and steady state concentrations) with the patch was about 60% higher than a combined OC with 35 mcg ethinyl estradiol and 0.25 norgestimate, although peak concentrations are about 25% lower. This information, which has been added to product labeling, has caused uncertainty regarding safety of the patch with respect to estrogen content and associated thromboembolic risk. Epidemiological data is limited to one published and one unpublished study, with conflicting results.

Adverse effects with the vaginal ring – Adverse effects with the vaginal ring appear low compared to rates typically reported with combined OCs. Overall, 5-14% of women reported the most common adverse effects (vaginitis, headache, vaginal secretion, weight gain, and nausea). A cross-over study focusing on genital symptoms (Veres et al, 2004) showed a higher percentage of women reporting vaginal wetness during ring use compared to a combined OC (63% vs. 43%), but did not find evidence of any pathological conditions associated with ring use. Specific to the vaginal ring are issues such as interference with intercourse (about 85% of women and 71% of partners say they cannot feel the device during intercourse), premature expulsion (occurring in about 0.5% of cycles), and lack of comfort with inserting and removing the vaginal ring (which does not require exact positioning). After insertion, the product remains effective for about 35 days, providing a safety margin if the patient fails to remove the ring on schedule and making extended or continuous use feasible.

DoD providers surveyed cited advantages of the vaginal ring as being improved compliance with infrequent dosing and a good adverse effect profile; disadvantages included a substantial number of patients who are not comfortable with the method and deployment limitations related to storage requirements.

Adverse effects with DMPA injections – Women receiving injectable DMPA may lose significant bone mineral density, an effect which may not be completely reversible. It is unclear whether use during adolescence or early adulthood reduces peak bone mass and increases the risk of osteoporotic fracture in the future. Injectable DMPA products carry a black box warning advising that it be used as a long-term birth control method (e.g., longer than two years) only if other birth control methods are inadequate.

Of the contraceptives reviewed, only injectable DMPA appears to be associated with progressive (and substantial) weight gain, with labeling for the 150 mg IM strength reporting an average weight gain of 5.4 lb in women completing 1 year of treatment, 8.1 lb after 2 years,

13.8 lb after 4 years, and 16.5 lb after 6 years. Labeling for the 104 mg SQ strength provides one-year results from three large clinical trials (average weight gain 3.5 lbs in the first year of use) and 2-year results from a small study comparing the two strengths (average weight gain of about 7.5 lbs with either strength).

Other issues with DMPA injections include amenorrhea in a high percentage of users (may be an advantage or disadvantage); irregular menses and unpredictable spotting/bleeding in the first several months of use; and lack of immediate reversibility (10 months to return to baseline fertility).

Drug interactions – A large number of medications may interact with hormonal contraceptives. Oral contraceptives may also affect levels of other medications. Data do not suggest a higher incidence of clinically significant drug interactions based on differences in progestogen content, phasic formulation, regimen, or route of administration.

Use in special populations – There are multiple considerations which may affect the choice of contraceptives in women with concomitant conditions (e.g., endometriosis). Progestogen-only OCs may be preferred in women who are breastfeeding, due to concerns about estrogen effects on the content and quality of breast milk, and the potential for infant exposure.

5) Other Factors – One practical concern with the vaginal ring is storage. Refrigeration is required prior to dispensing. After dispensing, the product may remain at controlled room temperature for up to 4 months, but should not be exposed to excessive heat. Heat, humidity, and exercise may also affect adhesion of the transdermal patch.

6) Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that: 1) contraceptives vary in estrogen and progestogen content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices based on estrogen and progestogen content consistent with variable patient response and the clinical niches for which multiple are required; 6) the alternative formulations (vaginal ring, patch, IM and SQ injection) are required for adequate clinical coverage; and 7) none of the reviewed contraceptives are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical conclusion as stated above.

B. Contraceptive UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the contraceptive agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

The clinical review identified 35 unique contraceptive entities, the majority of which are available generically. For clinical comparison, these agents were classified into one of 11 categories based upon their estrogen content, phasic formulation, or route of administration. This classification system was also used in the economic review. However, for the initial cost assessment, the contraceptives were stratified into three broad groups: 1) OCs available only as brand-name products; 2) OCs available generically; and 3) non-oral contraceptives.

Respectively, these groups represented 20%, 53%, and 27% of the total annual contraceptive drug spend.

The initial cost assessment was based on average weighted cost per cycle across the MHS. This assessment found generically available oral contraceptives to be, in general, more cost-effective than brand name oral contraceptives and non-orally administered contraceptives. Additionally, it was determined that further opportunity exists to obtain lower prices for generic agents through national pharmaceutical contracts. For these reasons, the P&T Committee concluded that all generically available contraceptives should be maintained on the UF.

The P&T Committee also concluded that despite a somewhat higher average weighted cost per cycle for non-orally administered contraceptives (Nuvaring, Ortho Evra, Depo-Provera and equivalents, Depo-subq Provera 104) compared to generically available OCs, these agents should remain on the UF to ensure clinical coverage for patients who need these methods of administration. Likewise, the P&T Committee concluded that Plan B should remain on the UF, because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception. The P&T Committee also discussed availability of Plan B from the TMOP, which currently does not fill prescriptions for Plan B. Although Plan B must be used within 72 hours of unprotected intercourse to be effective, which is not possible via mail order, the P&T Committee agreed that: (1) Under 32 CFR 199.21(h)(2)(i), formulary pharmaceutical agents are required to be available under the Pharmacy Benefits Program from all four points of service identified in paragraph 199.21(h)(1), except for military treatment facilities which are required only to have available BCF agents, with other formulary agents based upon their scope of practice; (2) consistent with this requirement, other medications which must be used acutely are available through mail order (e.g., antibiotics); and (3) this requirement of availability through mail order can ameliorate access problems.

A CMA and BIA were performed to determine the relative cost-effectiveness of the brand name oral contraceptives. The comparators for these analyses were the OCs within the same subgroup (as defined by the clinical review) as the brand name agent being analyzed. The brand name contraceptives considered in these analyses were: Estrostep Fe, Ovcon-35, Ovcon-50, Yasmin, Yaz, Ortho Tri-Cyclen Lo, and Seasonale.

The results of each category-specific CMA were incorporated into a BIA to account for other factors and costs associated with a potential decision to recommend non-formulary status for one or more brand-name contraceptive agents. The BIA accounted for market share migration, cost reductions associated with non-formulary cost shares, and medical necessity processing fee. Based on the CMA and BIA results of the combined category-specific analyses, the P&T Committee agreed that Yasmin, Yaz, and Ortho Tri-Cyclen Lo offered clinical and/or economic value for retention on the UF. The P&T Committee agreed that Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be non-formulary, because the category-specific cost-minimization analyses showed clinically similar alternatives were available at a significantly lower cost.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the UF cost analysis presented by the PEC. The P&T Committee concluded that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) were not cost-effective relative to other contraceptive agents with similar clinical attributes. Taking into consideration the conclusions from the relative clinical effectiveness and relative

cost-effectiveness determinations of the contraceptive agents, and other relevant factors, the P&T Committee recommended that Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary under the UF, and that Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, Plan B, and all generically available OCs be retained on the UF (See Table 1 on Pages 19-20 for a complete list of generically available OCs).

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified non-formulary under the UF, with Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically available contraceptives (and equivalents) being added to the UF. In a separate vote, the P&T Committee recommended (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF.

The P&T Committee also voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP; with a quantity limit of one Plan B package per copay applying to prescriptions filled by TMOP and retail network pharmacies.

C. Contraceptive Agents UF Medical Necessity Criteria: Based on the clinical evaluation of contraceptive agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for the combined OCs that were recommended for non-formulary status:

1) Use of formulary combined OCs is contraindicated.

2) The patient has experienced significant adverse effects from formulary combined OCs, or is likely to experience significant adverse effects from formulary combined OCs, and is expected to tolerate a non-formulary contraceptive agent.

3) Use of formulary combined OCs has resulted in therapeutic failure.

The P&T Committee agreed that it was extremely unlikely that a non-formulary contraceptive agent would truly be medically necessary, given the number and variety of contraceptive agents recommended for formulary status and the inclusion of contraceptives that are very similar to the recommended non-formulary agents.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to approve the medical necessity criteria.

D. Contraceptive Agents UF Implementation Plan: Because a high proportion of beneficiaries who would be affected by this formulary action are receiving Seasonale, which necessarily requires a 90-day prescription (about 11,000 DoD beneficiaries receive one or more prescriptions for Seasonale annually, out of about 23,000 patients with one or more prescriptions annually for Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe), the P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and

2) medical necessity is established. MTFs may (but are not required to) fill a prescription for non-formulary contraceptives written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Contraceptive Agents BCF Review and Recommendations

The P&T Committee had previously determined that at least one but no more than two contraceptive products would be added to the BCF in each of the following subgroups. The P&T Committee could also consider addition of contraceptives in other subgroups, if needed. Based on the relative clinical effectiveness and cost effectiveness of the agents within each subgroup recommended for UF addition and taking into account the desire to maximize clinical coverage by providing a wide array of products within the most commonly used subgroups, the P&T Committee recommended the following OCs for BCF status.

- *Monophasic OCs with 20 mcg EE*
  - EE 20 mcg; 3 mg drospirenone (Yaz)
  - EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- *Monophasic OCs with 30 mcg EE*
  - EE 30 mcg; 3 mg drospirenone (Yasmin)
  - EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- *Monophasic OCs with 35 mcg EE*
  - EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
  - EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- *Triphasic OCs*
  - 25 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
  - 35 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- *Progestogen-only OCs*
  - 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

The P&T Committee extensively discussed addition of the vaginal ring product (Nuvaring) to the BCF. Factors supporting addition included potential compliance advantages with once monthly dosing, a low adverse effect profile, and positive provider comments. The major factor opposing addition was the P&T Committee's uncertainty as to whether the clinical advantages outweighed the substantially higher cost per cycle compared to the OCs recommended for the BCF. The P&T Committee ultimately voted not to recommend Nuvaring for the BCF (6 for, 7 opposed, 2 abstained, 3 absent).

The P&T Committee noted that BPA prices submitted by manufacturers contingent upon UF and BCF status had a substantial impact on cost-effectiveness, particularly for some of the brand-name products (e.g., Yasmin, Yaz, and Ortho Tri-Cyclen Lo), which resulted in BCF recommendations that should broaden clinical coverage and reduce the unit cost of these widely used contraceptive products at MTFs. MTFs considering formulary status for products previously on the BCF should take into consideration local needs, as well as the potential that further cost reductions for generically available products may result from national contracting initiatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following contraceptive agents for the BCF:

- EE 20 mcg; 3 mg drospirenone (Yaz)
- EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- EE 30 mcg; 3 mg drospirenone (Yasmin)
- EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
- EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- EE 25 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
- EE 35 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

10. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on May 10, 2006. The dates of the next meeting are August 15-17, 2006.

_____signed_____
Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 06	OABs	tolterodine IR (Detrol) oxybutynin patch (Oxytrol) trospium (Sanctura)	BCF	oxybutynin IR (Ditropan tabs/soln) tolterodine SR (Detrol LA)	26 Apr 06	26 July (90 day implementation period)	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	26 Apr 06	26 July (90 day implementation period)	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	26 Apr 06	28 Jun (60 day implementation period)	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs May 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Insulin detemir Injection (Levemir); Novo Nordisk**;** long-acting insulin	Jun 05: Treatment of insulin dependent diabetes mellitus in adults requiring long acting insulin for control of hyperglycemia. Oct 05: Treatment of pediatric Type I DM	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Insulin glulisine injection (Apidra); Sanofi-Aventis; ultra short acting insulin analogue	Apr 04: Treatment of insulin dependent diabetes mellitus in adults requiring ultra short acting insulin for control of hyperglycemia	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Ranolazine tablets (Ranexa); CV Therapeutics**;** partial fatty oxidase inhibitor	Jan 06: Treatment of chronic angina when used in combination with amlodipine, beta blockers or nitrates	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the miscellaneous cardiovascular drug class is reviewed.
Sunitinib capsules (Sutent); Pfizer**;** multi-kinase inhibitor	Dec 05 (priority review); Treatment of gastrointestinal stromal tumor after disease progression on, or intolerance to, imatinib (Gleevec). Treatment of advanced renal cell carcinoma	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed. Quantity limits recommended: TMOP: 50 mg: #60 caps/84 days, 25 mg: #120 caps/84 days, 12.5 mg: #180 caps/84 days. Retail Network: 50 mg: #30 caps/30 days, 25 mg:#60 caps/30 days, 12.5 mg: #120 caps/30 days
Lenalidomide capsules (Revlimid); Celgene**;** immunomodulatory drug (thalidomide analogue)	Dec 05: Treatment of myelodsyplastic syndromes in transfusion dependent patients with del 5q cytogenetic abnormality	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed.
Mecasermin rinfabate injection (Iplex); Insmed Pharmaceuticals; recombinant human insulin-I-like growth factor-1 (IGF-1)	Aug 05: Long-term treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until growth hormone / IGF-1 drug class is reviewed. Added to existing PA criteria and forms for mecasermin (Increlex).

Appendix C – Table 3. Table of Abbreviations

5-HT3	type 5 serotonin antagonists
ACOG	American College of Obstetricians and Gynecologists
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DEA	Drug Enforcement Administration
DMPA	depot medroxyprogesterone acetate
DoD	Department of Defense
EE	ethinyl estradiol
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
GIST	gastrointestinal stromal tumor
H2	histamine-2
IV	intravenous
MHS	Military Health System
MTF	military treatment facility
NK-1	neurokinin-1
NNT	number needed to treat
OCs	oral contraceptives
ODT	orally dissolving tablet
PA	prior authorization
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PONV	post-operative nausea and vomiting
RINV	radiation-induced nausea and vomiting
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary
VTE	venous thromboembolism

DECISION PAPER:

FEBRUARY 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on two new agents that had been approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. It is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days from the TRRx. (See paragraph 5 on pages 10-11 of P&T Committee minutes.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the antimuscarinic drugs used to treat over active bladder. The overactive bladder therapeutic class was defined as: oxybutynin immediate release (Ditropan tablets/solution or generic) oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine immediate release (Detrol), tolterodine sustained release (Detrol LA), trospium (Sanctura),

solifenacin (Vesicare), and darifenacin (Enablex). This class is now ranked 28th in Military Health System (MHS) drug class expenditures at a cost of $55 million annually.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review none of the OABs have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other OABs.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee agreed (15 for, 0 opposed, 0 abstention, 3 absent) that a group of OAB agents including tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin, and darifenacin represented the best overall value to the DoD for the treatment of OAB across all three points of service.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin and darifenacin classified as formulary on the UF. (See paragraphs 6A and 6B on pages 11-16 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of tolterodine immediate release, oxybutynin patch, trospium and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the OAB agents. (See paragraph 6C on pages 16-17 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 6D on page 17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☐Approved ☑ Disapproved

~~Approved, but modified as follows~~: *"I note that the BAP recommended a 120 day implementation period. I have increased the implementation period to 90 days."*

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oxybutynin immediate release and tolterodine sustained release as the Basic Core Formulary (BCF) agents. (See paragraph 6E on page 17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The class was defined to include the angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/trandolapril (Tarka); the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists (clonidine, methyldopa, guanabenz, guanfacine); the peripheral alpha-1 antagonists (prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers (mecamylamine). Together these drugs account for approximately $27M annually and are ranked 53rd in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) there is no evidence that any one ACE/CCB combo is more effective relative to another for lowering blood pressure; (2) there is more evidence to support the use of amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/enalapril; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4) safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril may be improved by 7%-22% compared to the individual agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the UF due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

Based on the results of the CEA and other clinical and cost considerations, the Committee agreed (16 for, 0 opposed, 1 abstention, 1 absent) that a group of miscellaneous antihypertensive agents including amlodipine/benazepril, the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists [(clonidine tablets and patches), methyldopa, guanabenz, guanfacine]; the peripheral alpha-1 antagonists (prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers

(mecamylamine) represented the best overall value to the DoD in the class of miscellaneous antihypertensive agents.

A. COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril (Lexxel) and verapamil/trandolapril (Tarka) be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril (Lotrel), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF. (See paragraphs 7A and 7B on pages 18-24 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows: *"I note the BAP's concern about having Lotrel as UF agent when amlodipine is non-formulary. 50K beneficiaries use Lotrel. Keeping this drug on the UF maintains the option of an ACE/CCB combo for these and other beneficiaries."*

B. COMMITTEE ACTION: Based on the clinical evaluation of felodipine/enalapril (Lexxel) and verapamil/trandolapril (Tarka) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for these agents. (See paragraph 7C on page 24 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 7D on page 24 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☐Approved ☑ Disapproved

~~Approved, but modified as follows~~: *"I note that the BAP recommended a 120 day implementation period. I have increased the implementation period to 90 days."*

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to recommend one combination agent [amlodipine/benazepril (Lotrel)] and two single agents (hydralazine and clonidine tablets) as the BCF agents. (See paragraph 7E on page 24 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

The DoD P&T Committee evaluated the relative clinical effectiveness of the GABA-analog agents marketed in the United States. The class was defined to include gabapentin (Neurontin and various generics), pregabalin (Lyrica) and tiagabine (Gabatril). Although gabapentin, pregabalin, and tiagabine all have FDA indicates as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused most heavily on the use of these agents for the treatment of various types of neuropathic pain. Together these drugs account for approximately $148M annually and are ranked 6th in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) the efficacy of gabapentin and pregabalin for treating pain associated with either diabetic peripheral neuropathy (DPN) or post-herpetic neuropathy (PHN) appears similar; (2) gabapentin is the only GABA-analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for use as adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status. Overall the Committee agreed based on clinical usefulness alone, there was no basis for classifying any of the GABA analogs as non-formulary.

Based on the results of the clinical and cost-effectiveness analyses, the Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF. (See paragraphs 8A and 8B on pages 24-31 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows: *"I agree with the concerns noted by some BAP members re off-label use of new drugs as first-line therapy when there are "tried and true" alternatives with known safety profiles. Lyrica remains available to those who need it under medical necessity criteria."*

B. COMMITTEE ACTION: Based on the clinical evaluations of pregabalin and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 1 opposed, 0 abstained, 2 absent) medical necessity criteria for the GABA-analog agents. (See paragraph 8C on pages 31-32 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 3 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8D on page 32 of P&T Committee minutes for rationale.).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend gabapentin as the BCF agent. (See paragraph 8E on page 32 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews of each class were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

APPENDIX A – TABLE 1. Implementation Status of UF Decisions

APPENDIX B – TABLE 2. Newly Approved Drugs

APPENDIX C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____//signed//_____
William Winkenwerder, Jr., M.D.
Date: 26 April 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

17 February 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14 February 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CDR Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
MAJ Paul Garrett MC *for* COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MS *for* COL Isiah Harper, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TRRx/TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Joel Schmidt, MC	Army, Physician at Large
COL Isiah Harper, MS	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MS, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA

Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Dan Remund	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
Catherine Kelly	Department of Veterans Affairs
Charles R. Brown	TMA/CMB

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – November 2005 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. November minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the November 2005 DoD P&T Committee on 19 January 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing: CAPT Buss, LtCol Bennett and LtCol Crownover briefed the members of the DoD P&T committee regarding the 15 December 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions: Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since

February of 2005 (see Appendix A – Table 1). The Committee made the following observations:

- Utilization in all UF classes remains stable suggesting continued access to drugs within the reviewed classes.
- Collectively, as a percent of prescriptions dispensed, utilization of UF agents across all reviewed drug classes and points of service (MTF, mail, retail) have increased, while utilization of non-formulary agents has decreased. Among the UF decisions that have been implemented since the first UF DoD P&T meeting in February 2005 DoD there has been a 34% reduction in the use of non-formulary agents. Among all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been a 17% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
    - Formulary decisions resulting in a higher degree of drug class restrictiveness (i.e., phosphodiesterase-5 inhibitors) are generating better market share results than formulary decisions allowing multiple UF options within a drug class (i.e., angiotensin receptor blockers).
    - Market shares by point of service reflect the degree of utilization management applied to each point of service. The more highly managed points of service (ie., MTF, mail) are generating higher market shares of UF agents than the unmanaged point of service (i.e., retail).
- Overall market share projections for UF agents of 80% have not yet been realized. Although these projections were based on an implementation plan utilizing a one year time horizon, it is unlikely this degree of conversion will be achieved across all three points of service.
    - Models used to describe the relative economic comparison of agents within a drug class have been adjusted to reflect this information.
    - For the February 2006 drug classes evaluated for UF status, switch rates were reduced from 80% at all three points of service to approximately 70% at the MTF point of service and 30% in the retail and mail order sectors.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on two new agents recently approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. Sorafenib is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) do have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system

which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days (TRRx).

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW.

A. OAB Medications Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved antimuscarinic drugs available in the U.S. for the treatment of overactive bladder. The OAB therapeutic class was defined as the antimuscarinics: oxybutynin immediate release (Ditropan tablets/solution or generic), oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine immediate release (Detrol), tolterodine sustained release (Detrol LA), trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve month period ending 30 Sept 2005, 147,508 Military Health System (MHS) patients were prescribed an antimuscarinic drug for overactive bladder. This class is now ranked 28th in MHS drug class expenditures at a cost of $55 million annually.

1) Efficacy

Efficacy measures. The antimuscarinic drugs reviewed are FDA-approved for the treatment of OAB. Efficacy measures used in clinical trials include the following:

a. Weekly number of urge incontinence episodes and total (urge plus non-urge) urinary incontinence episodes
b. Daily micturition frequency for up to 7 consecutive days during the baseline period and for one or more periods prior to clinic visits
c. Daily frequency of urgency episodes
d. Daily severity of urgency episodes
e. Volume voided per micturition
f. Number of incontinence episodes resulting in a change of pad or clothing per week
g. Nocturnal awakenings per week due to OAB symptoms
h. Volume to first urge sensation
i. Volume to first detrusor contraction
j. Bladder capacity (volume)
k. Post-void residual volume

Efficacy results: No differences in efficacy were reported when the following trials were assessed: four studies comparing oxybutynin immediate release and tolterodine immediate

release; one study of trospium versus oxybutynin immediate release; four studies of oxybutynin sustained release versus oxybutynin immediate release; and one study comparing of tolterodine sustained release versus tolterodine immediate release.

Oxybutynin sustained release was found to be superior to tolterodine immediate release in one trial; conversely tolterodine sustained release was reported as superior in one comparative trial against oxybutynin immediate release. Conflicting results were reported in the trials comparing oxybutynin sustained release and tolterodine sustained release, however, the two products showed similar efficacy in the comparative clinical trial that had the most rigorous study design. Solifenacin (flexible dose) showed greater efficacy over tolterodine sustained release (fixed dose) in one trial, however the results may be explained by lack of dosage titration allowed in the tolterodine sustained release group. Another short term trial showed greater efficacy with solifenacin vs tolterodine immediate release in some, but not all, efficacy measures. There were no trials comparing darifenacin vs. other OAB drugs.

A comparison of the OAB drugs' effects on the primary efficacy was made by adjusting for placebo effect and standardizing for 24 hour results. This comparison was not designed to demonstrate superiority, but designed to provide a range of improvement. All of the OAB agents decreased incontinence episodes by 0.32 - 1.04 events per 24 hours and urinary frequency by 0.6 - 1.3 voids per 24 hours.

Efficacy conclusion: In controlled clinical trials in overactive bladder, there was a high placebo efficacy rate. All of the OAB drugs have shown statistical superiority over placebo in controlled trials, however the results are of questionable clinical significance. Despite the availability of several head-to-head comparative trials for the OAB drugs, it is difficult to determine superiority of one product over another, due to differences in study design. When the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another.

2) Safety and Tolerability

Contraindications: All the OAB drugs carry a similar contraindication of use in patients with gastric retention, urinary retention and uncontrolled narrow angle glaucoma.

Serious side effects: Irreversible urinary retention is a possible serious side effect with all the drugs in the OAB class. Cases are rare especially with the use of long acting agents.

Common Side effects: The majority of the side effects are due to the anti-cholinergic properties inherent to the class. The most prevalent side effects are dry mouth, constipation, dry eyes, somnolence and nausea. The newer agents (solifenacin, darifenacin and trospium) cause similar rates of dry mouth as the older agents (tolterodine and oxybutynin). These newer OAB drugs cause more constipation than tolterodine and oxybutynin. In the clinical trials with the oxybutynin patch, patients treated with the patch had a lower anti-cholinergic side effect profile verses patients receiving tolterodine and oxybutynin oral formulations. However, the patch was associated with significant dermatological side effects resulting in patient withdrawal. Oxybutynin immediate release is listed on the Beer's Criteria indicating the drug's use should be limited in the elderly.

Evidence from short-term head-to-head comparison trials indicate a higher incidence of adverse events overall, and dry mouth specifically, with oxybutynin. The sustained release forms of each drug resulted in fewer adverse events and dry mouth when compared to formulations. Trospium causes less severe dry mouth although the overall incidence of dry mouth and short

term adverse events are similar to oxybutynin immediate release. The difference between drugs based on withdrawals is less clear. Two trials of solifenacin versus tolterodine showed similar rates of adverse events overall; one trial showed lower rates of dry mouth for tolterodine sustained release versus solifenacin.

Discontinuation Rates: One comparative long-term study assessed the discontinuation rate of tolterodine and oxybutynin immediate release over a 6-month period. Oxybutynin immediate release treatment resulted in a higher discontinuation rate and earlier withdrawal from therapy than patients receiving tolterodine. The discontinuation rates and withdrawal rates were high for both drugs. Uncontrolled studies reported that dry mouth is the most common adverse event, and found similar rates of adverse events and withdrawals between oxybutynin and tolterodine. One head-to-head trial of trospium versus oxybutynin reported more adverse effects attributed with oxybutynin, especially dry mouth.

Drug interactions: There is the potential for induction or inhibition of hepatic cytochrome P450 isoenzymes with all the OAB drugs except trospium. There are few studies evaluating the clinical effects of these drug interactions. All the OAB drugs have the potential to increase the anti-cholinergic effects when used concomitantly with other anti-cholinergic drugs, which increases the risk for adverse effects and toxicity. All the OAB drugs can potentially increase the risk for sedation when taken with other drugs with sedating effects.

Persistence: Persistence rates of less than 10% with the OAB drugs have been reported in the literature. In the MHS, after a 12 month evaluation period, the persistence rates for tolterodine sustained release, oxybutynin sustained release, and oxybutynin immediate release were 5% to 16%. There were insufficient numbers of prescriptions refilled for the three newest OAB drugs to determine persistent rates. MHS beneficiaries using TMOP were more persistent with OAB therapy than those beneficiaries using other points of service. Noted in the study were a number of patients refilling OAB drug prescriptions well after the due date. It is possible that patients are using the OAB drugs on an as needed basis as dictated by social situations

Safety/tolerability conclusion: Anti-cholinergic effects are the most bothersome adverse events with all the OAB drugs. The most frequently encountered adverse event is dry mouth, which occurs with a higher rate for immediate release formulations than with SR formulations. The highest frequency of dry mouth occurs with oxybutynin immediate release. The three newest OAB drugs (trospium, solifenacin, and darifenacin) do not substantially lower the rate of dry mouth compared with tolterodine or oxybutynin sustained release, but do cause a higher rate of constipation. An evaluation of prescription refill patterns in DoD shows low persistence rates with tolterodine and oxybutynin. There was not enough data available to adequately evaluate MHS persistence rates for trospium, solifenacin, and darifenacin.

3) Other Factors

Dosing: All of the agents in the class are dosed once daily except for trospium, oxybutynin immediate release, and tolterodine immediate release. Once daily dosing theoretically increases compliance. Oxybutynin sustained release is frequently dosed in a range of 5 mg to 15 mg daily in clinical trials. In contrast, DoD usage shows 20 mg to 30 mg daily more commonly used, which can potentially increase the risk of adverse events.

Special populations: Pediatrics: Oxybutynin immediate release and sustained release are FDA-approved for use in children 6 years and older. The manufactures of tolterodine are pursuing an indication for use in pediatric patients.

Pregnancy: All the OAB drugs are rated as pregnancy category C with the exception of oxybutynin which is rated category B.

DoD Provider Comments: DoD providers were most comfortable prescribing oxybutynin immediate release and tolterodine sustained release; these two drugs have been included on the BCF since 2002. Most providers favored tolterodine sustained release. A majority of respondents had heard of the newer agents, trospium, solifenacin and darifenacin, but over 80% had not yet prescribed the agents. Most providers reported that the side effect profiles seen with clinical usage were similar to what is reported in the literature. DoD providers overestimated MHS persistence rates at 43% compared to the actual rates of between 5% and 16%.

Other Factors Conclusion: There is no evidence to suggest clinical superiority of any one OAB drug over another based on differences in dosing and titration schedules or DoD provider opinion. For pediatric patients, oxybutynin is preferred at this time.

Overall Clinical Effectiveness Conclusion: The DoD P&T Committee concluded that: 1) when the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another; 2) When similar dosage forms are compared (immediate release to immediate release; sustained release to sustained release) the side effect profiles are similar; 3) immediate release forms of the overactive bladder drugs induce more anti-cholinergic side effects than the sustained release forms; 4) the new agents, solifenacin and darifenacin, and trospium have an increased rate of constipation compared to oxybutynin sustained release and tolterodine sustained release; 5) oxybutynin is the only product which is approved for use in children at this time; 6) MHS persistence rates with all drugs in this class are very low, ranging between 16% and 55% at the end of a one year evaluation period; 7) DoD providers were most comfortable prescribing oxybutynin and tolterodine and had little experience with the newer agents.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review, all the drugs reviewed for OAB were similar in terms of effectiveness and clinical outcome.

B. OAB UF Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the OAB agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e) (2).

To determine the relative cost effectiveness of the OAB agents, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding evidence-based relative clinical effectiveness evaluation, the P&T Committee concluded that, when comparing immediate release agents to immediate release agents and sustained release agents to sustained release agents, there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB. Normally, such a conclusion would suggest cost-minimization to be the appropriate pharmacoeconomic analysis, however, in this case, to account for the differences in relative clinical effectiveness between the immediate release and sustained release agents in this therapeutic class, a cost-effectiveness analyses (CEA) was used. This was done based on the results of a sample based retrospective cohort database analysis. In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes).

A one-year sample-based retrospective cohort database analysis was performed on DoD MHS prescription data. The study population was comprised of DoD patients filling prescriptions for oxybutynin immediate release, oxybutynin sustained release, oxybutynin patch, tolterodine immediate release, tolterodine sustained release, and trospium between 01 July 2004 and 30 September 2005. Patients taking any OAB agent, in the 6 month period prior of their observed period of enrollment, were excluded to capture new users only. Note, darifenacin and solifenacin were not included in the study since these agents are new and lacked a year's worth of utilization data. The drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service) and the outcome of interest was adherence to treatment, where adherence to treatment was measured by total days of treatment. Theoretically, adherence to treatment is a surrogate indicator of efficacy, safety, and tolerability. In other words, a patient is more inclined to adhere to treatment if the agent works (efficacy) and is tolerated to the extent that the benefits of treatment outweighs the risk of side effects (tolerability and/or safety).

The results from the sample-based retrospective cohort database analysis were incorporated into a CEA. The cost used in the analysis for each agent was the mean cost of treatment for one year and the effect/outcome was the mean days of treatment for one year. Overall, the results of the CEA were as follows:

- Overall, oxybutynin immediate release was determined to be the most cost-effective agent and tolterodine sustained release was determined to be significantly more costly and effective along the efficiency frontier.
- Among the multi-dosed immediate release agents, oxybutynin immediate release was determined to be the most cost-effective agent; tolterodine immediate release was determined to be slightly more effective but significantly more costly (> 15-fold) compared to oxybutynin immediate release; and trospium immediate release was determined to be slightly less effective and significantly more costly (> 15-fold) compared to oxybutynin immediate release
- Among the once daily extended release agents, tolterodine sustained release was determined to be the most cost-effective agent; oxybutynin patch and sustained release tablet were dominated (more costly and less effective) compared to tolterodine sustained release.

Although the evidence-based relative clinical effectiveness evaluation determined that there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB, this CEA based on a sample-based retrospective cohort database analysis suggests that differences do exist among the agents in regards to adherence to treatment.

Since darifenacin and solifenacin lacked sufficient utilization data to be included in the CEA analysis, the agents were evaluated on their point of service adjusted total weighted average cost per day of treatment only. The manufacturers of darifenacin and solifenacin submitted highly competitive prices for their respective agents, which made them significantly less costly compared to the most cost-effective single-dosed extended release agent, tolterodine sustained release. For purposes of this evaluation, the DoD P&T Committee assumed that darifenacin and solifenacin would have similar relative clinical effectiveness compared to tolterodine sustained release, based upon the conclusion of the overall relative clinical effectiveness presentation.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of OAB agent's best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations (oxybutynin sustained release is projected to go generic in 2006), the Committee agreed that a group of OAB agents that included: darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release best achieved this goal when compared to other combination groups of OAB agents, and thus were determined to be more cost-effective relative to other combination groups.

*Conclusion**:*** The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 2 abstention, 1 absent) to accept the OAB pharmacoeconomic analyses presented by the PEC. The P&T Committee concluded that: tolterodine immediate release, oxybutynin patch, and trospium were not cost-effective relative to the other OAB agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee recommended that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF, with darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release remaining on the UF. In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

C. OAB Drug UF Medical Necessity Criteria: Based on the clinical evaluation of overactive bladder drugs, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for these agents.

1) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) are contraindicated, and the use of tolterodine immediate release, trospium, or oxybutynin patch is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) and the patient is expected to tolerate tolterodine immediate release, trospium, or oxybutynin patch.

3) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) resulted in

therapeutic failure, and the patient is expected to respond to tolterodine immediate release, trospium, or oxybutynin patch (therapeutic failure as outlined on medical necessity form).

4) The patient has previously responded to the oxybutynin patch, and changing to the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) would incur unacceptable risk. The Committee agreed that this criterion could apply because of the potentially lower risk of CNS effects with the oxybutynin patch.

5) There is no alternative formulary agent: The Committee agreed that this criterion could apply to the oxybutynin patch if the patient could not take oral medications.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the medical necessity criteria.

D. OAB Drug UF Implementation Plan: Because of the low number of beneficiaries who would be affected by this formulary action (19,118 patients known to be taking tolterodine immediate release, trospium, or oxybutynin patch across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tolterodine immediate release, trospium, or oxybutynin patch on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for tolterodine immediate release, trospium, or oxybutynin patch written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. OAB Drug Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two overactive bladder drugs would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that oxybutynin immediate release and tolterodine sustained release be added to the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to include oxybutynin immediate release and tolterodine sustained release on the BCF.

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

A. Miscellaneous Antihypertensive Agents UF Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The drugs in the class included the angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/ benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/trandolapril (Tarka); the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists (clonidine, methyldopa, guanabenz, guanfacine); the peripheral alpha-1 antagonists

(prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers (mecamylamine). Information regarding the safety, effectiveness, clinical outcomes, and patient persistence rates of the ACE inhibitor/CCB combinations (ACE/CCB combos) was considered in depth. For the other miscellaneous antihypertensive agents, the Committee considered the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The clinical review included, but was not limited to, the requirements stated in the UF Rule.

1) *ACE inhibitor/CCB combinations:* The relative clinical effectiveness of the individual ACE inhibitors and calcium channel blockers was reviewed previously by the Committee. Refer to the minutes from the August 2005 P&T Committee meeting for the relative clinical effectiveness conclusion for these two drug classes.

   a) Pharmacology: Both amlodipine/benazepril and felodipine/enalapril contain a dihydropyridine (DHP) CCB. The verapamil component of verapamil sustained release /trandolapril is a non-dihyropyridine CCB. Verapamil reduces myocardial contractility and slows conduction through the atrioventricular node. The physiologic effect of slowed heart rate with the non-DHP CCBs is frequently used as a beneficial effect in patients with increased heart rate (e.g. atrial fibrillation). The DHPs do not slow cardiac conduction, but have peripheral vasodilatory effects. The individual ACE inhibitor components of the combo products (benazepril, enalapril, trandolapril) exhibit similar pharmacologic properties.

   The benefits of combining an ACE inhibitor with a CCB include additive blood pressure (BP) lowering effect due to differing mechanisms of action, attenuation of CCB-induced edema through addition of the ACE inhibitor, patient convenience due to simplified drug regimens, decreased pill burden, and potentially improved adherence with antihypertensive therapy.

   b) Efficacy for Hypertension:

   Place in Therapy: The three ACE/CCB combinations are all approved for the treatment of mild to moderate hypertension. The Joint National Commission VII (JNC VII) guidelines acknowledge that combination antihypertensive therapy may be necessary, and is likely to be used as first-line treatment of hypertension. The guidelines recommend use of a combination regimen, which should usually include a diuretic, as first-line therapy for stage 2 hypertension (BP $\geq$160/100 mm Hg), or for patients with compelling indications. Compelling indications for use of an ACE inhibitor include heart failure, post-myocardial infarction, high risk of coronary artery disease, diabetes, chronic kidney disease, or previous stroke; compelling indications for use of a CCB include diabetes and patients with high risk of coronary artery disease.

   Efficacy for lowering BP: All three products have clinical trial data showing enhanced efficacy when the combination product is compared to the single components administered individually. Data from the individual package inserts was used to compare BP lowering effects. Amlodipine/benazepril reduces systolic blood pressure (SBP) by 10-25 mmHg and diastolic blood pressure (DBP) by 6-13 mmHg, felodipine/enalapril reduces SBP by 14.2 mmHg and DBP by 12.6 mmHg, and verapamil/trandolapril reduces SBP by 13-22 mmHg, and DBP by 8-17 mmHg.

Effects in sub- populations of patients with hypertension: There are no published trials of felodipine/enalapril (Lexxel) in sub-populations of patients with hypertension. Both amlodipine/benazepril and verapamil sustained release /trandolapril have several published trials supporting efficacy in patients with type 2 diabetes, patients with moderate to severe hypertension, and African Americans. Direct comparisons of BP lowering effects in the sub-populations are difficult, due to differences in study design.

Effect on proteinuria: The verapamil CCB component of verapamil sustained release/ trandolapril physiologically decreases resistance of the afferent renal arteriole, which reduces glomerular pressure and proteinuria. DHP CCBs do not have this effect on the afferent arteriole. Evidence from one large clinical trial showed that a combination of verapamil with trandolapril over a 3 year period prolonged the time to onset of microalbuminuria in patients with type-2 diabetes and hypertension.

Cardiovascular Outcomes: There are no published trials with felodipine/enalapril showing a benefit of the drug in reducing cardiovascular outcomes. There are no completed trials with amlodipine/benazepril assessing cardiovascular outcomes; two ongoing trials are assessing cardiovascular mortality/morbidity (ACCOMPLISH trial) and progression to overt nephropathy (GUARD). There are no published trials assessing the efficacy of the specific Tarka formulation at reducing cardiovascular outcomes. Although a regimen comprised of verapamil sustained release and trandolapril used as add-on therapy showed a reduction in all-cause death, non-fatal myocardial infarction, and non-fatal stroke (INVEST trial), this open label trial did not show a difference in outcomes between a regimen of CCB and ACE inhibitor vs. beta blocker and diuretic. The INVEST trial did not randomize patients prospectively to the combination, thus cannot be used to support efficacy of the specific Tarka formulation in reducing cardiovascular outcomes.

Clinical Efficacy Conclusion: The Committee concluded that there is insufficient evidence to suggest that the BP lowering effects of the ACE/CCB combos differ significantly. The formulations of amlodipine/benazepril and verapamil sustained release/trandolapril have shown efficacy in treating sub-populations of patients with hypertension; there is no data with Lexxel. Clinical trials assessing cardiovascular outcomes with the combination products Lexxel, amlodipine/benazepril and verapamil sustained release/trandolapril have not been conducted, but there is some evidence of benefit with the individual components.

c) Safety and Tolerability:

Serious Adverse Effects: Verapamil sustained release/trandolapril is contraindicated for use in patients with impaired cardiac contractility (e.g. severe left ventricular dysfunction, SBP < 90 mm Hg), due to the verapamil component. All three ACE/CCB combos are contraindicated for use in patients with a history of angioedema to any ACE inhibitor.

Common Adverse Effects: The safety profiles of the ACE/CCB combos are reflected by their individual CCB components. The products containing a DHP CCB (amlodipine/benazepril and felodipine/enalapril) commonly causes edema and headache, while the non-DHP CCB (verapamil sustained release/trandolapril) more commonly causes dyspnea, fatigue, and constipation. Comparison of the product labeling between amlodipine/benazepril and felodipine/enalapril do not suggest major differences in the incidence of edema, headache, or dizziness.

Discontinuations due to Adverse Effects: Pooled data from clinical trials was used to compare the products in terms of the percentage of patients discontinuing therapy due to

adverse events. For felodipine/enalapril, 2.8% of patients discontinued treatment vs. 1.3% with placebo, most commonly due to headache. The percentage of patients discontinuing therapy with amlodipine/benazepril was 4%, vs. 3% with placebo, most commonly due to edema. The discontinuation rate with verapamil sustained release/trandolapril was 2.6% vs. 1.9% with placebo, most commonly due to dyspnea and fatigue.

Safety and Tolerability Conclusion: The DoD P&T Committee concluded that the discontinuation rate due to adverse events appears similar between the three ACE/CCB combos, based on pooled analysis from placebo controlled trials. The non-DHP component of verapamil sustained release/trandolapril imparts unique risks of impaired cardiac contractility. There is no evidence that amlodipine/benazepril and felodipine/enalapril differ markedly in adverse event profiles.

d) Other Factors - Adherence/Persistence with antihypertensive therapy: For the purposes of this review, the measure used to define persistence is the medication possession ratio, which is calculated based on the daily possession of drugs. There are no published trials with felodipine/enalapril or verapamil sustained release/trandolapril showing improved rates of patient persistence. Data from two studies (one published, the other in abstract form) using pharmacy claims databases reported medication possession ratios ranging from 81%-88% with patients continuously refilling prescriptions for amlodipine/benazepril, compared to 69%-73.8% for regimens containing an ACE inhibitor and CCB administered as separate components.

Conclusion for Other Factors (Adherence/Persistence): Two database claims studies suggest that patient persistence with amlodipine/benazepril is improved by 7%-22%, compared to regimens containing an ACE inhibitor and CCB administered as separate components.

2) *Other Miscellaneous Antihypertensive Agents:* The Committee evaluated the other miscellaneous antihypertensive agents by considering the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The Committee also specifically evaluated the relative clinical effectiveness of clonidine tablets vs. clonidine patch.

a) Clonidine oral tablets vs. Clonidine transdermal patches: The JNC VII guidelines recommend clonidine as a second or third line choice for treating hypertension, due to adverse effects. Clonidine is frequently used for off-label indications, including treatment of menopausal symptoms, smoking cessation, pediatric behavioral problems, and alcohol or opiate withdrawal symptoms. Clonidine tablets require twice daily to three times a day dosing, and there is a high risk of rebound hypertension, if the tablets are abruptly discontinued. The clonidine patches are changed weekly and are associated with a lower risk of rebound hypertension, since plasma levels of drug slowly decline over a one-week period when the patch is removed. Other benefits of transdermal clonidine include that it is frequently used in patients with swallowing difficulties (e.g. stroke patients), its use can potentially improve compliance in patients requiring several drugs for BP control, and that its use can simplify the medication regimen in patients requiring several antihypertensive drugs. In the entire MHS, approximately 20,000 prescriptions for clonidine tablets are dispensed monthly, compared to 5,000 prescriptions for clonidine patches.

b) Remaining miscellaneous antihypertensive agents in the class: The remaining miscellaneous antihypertensive drugs in the class include hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, prazosin, reserpine, guanadrel, guanethidine, and

mecamylamine. All of these drugs are available in generic formulations and some no longer have marketed proprietary formulations (e.g. reserpine, guanethidine). Utilization of these drugs in the MHS is low (<5,000 prescriptions dispensed in fiscal year 2005), with the exception of hydralazine (40,000 Rxs), prazosin (22,000 Rxs), methyldopa (13,000 Rxs), and minoxidil (12,000 Rxs). Some of these products have been available for several decades; including reserpine, mecamylamine, hydralazine, methyldopa, and guanethidine, thus rigorously conducted clinical trials are not available.

Place in therapy: JNC VII guidelines support use of methyldopa, hydralazine, minoxidil, reserpine, and guanfacine as antihypertensive drugs, although clinical use is often limited due to tolerability issues. Methyldopa is commonly used for treating hypertension in pregnant patients, due to long-term studies supporting its safety. Hydralazine also has a role in treating symptoms of heart failure in patients who are intolerant of or who have contraindications to use of ACE inhibitors. Guanfacine is also utilized in the setting of pediatric patients with behavioral problems. Guanabenz is rarely used clinically (<500 Rxs dispensed in the MHS in fiscal year 2005), as it requires twice daily dosing and has bothersome side effects. Minoxidil is an option for patients with stage 2 hypertension (SBP 160-179 / DBP 100-109 mm Hg) who have not responded to conventional antihypertensive drug regimens. Reserpine has evidence from randomized controlled trials that it reduces cardiovascular mortality and morbidity (VA trials, SHEP trials). Use of prazosin as an antihypertensive agent has fallen into disfavor, based on the results of the ALLHAT trial that showed an increased risk of development of heart failure in patients receiving the alpha blocker doxasozin. Guanadrel, guanethdine, and mecamylamine are rarely used today.

Adverse Effects: The use of the other miscellaneous antihypertensive agents has largely been replaced by other drugs (e.g. ACE inhibitors, diuretics, CCBs, angiotensin receptor blockers, beta blockers) due to their side effect profiles. Hydralazine may cause drug-induced systemic lupus erythematosus. Minoxidil can cause hypertrichosis; and fluid retention and reflux tachycardia are frequent problematic effects. Common adverse effects of methyldopa, guanabenz and guanfacine include fluid retention, sedation, lethargy, postural hypotension, dizziness, dry mouth and headache. First-dose syncope is a risk with prazosin and other alpha blockers. Clinical use of reserpine is limited due to nasal stuffiness and the perception of increased risk of depression. Orthostatic hypotension is an issue with guanadrel and guanethidine, as is diarrhea, and sexual dysfunction. Postural hypotension is a limiting side effect of mecamlyamine. Other effects of mecamylamine due to its ganglionic blockading properties include tachycardia, mydriasis, paralytic ileus, syncope, and urinary retention.

COMMITTEE RECOMMENDATION: *Overall clinical effectiveness conclusion for the miscellaneous antihypertensive agents:* The Committee concluded that: (1) for lowering blood pressure, there is no evidence that any one ACE/CCB combo is more effective relative to another; (2) there is more evidence to support the use of amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/ enalapril; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4); the safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril may be improved by 7%-22% compared to the individual

agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the UF due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 absent; 1 abstain) to accept the clinical effectiveness conclusion as stated above.

B. Miscellaneous Antihypertensives UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the miscellaneous antihypertensive agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e) (2).

As with the relative clinical effectiveness evaluation, the primary focus of the relative cost-effectiveness presentation was limited to the combination antihypertensives (amlodipine/benazepril, felodipine/enalapril, verapamil/trandolapril) and clonidine patches. The DoD P&T Committee concluded that the other agents listed in the class, as previously described, should be maintained on the UF given their generic availability, low utilization, and low cost.

To determine the relative cost effectiveness of the miscellaneous antihypertensive agents, two separate economic analyses were performed, a pharmacoeconomic analysis and BIA.

A cost analysis was performed to compare clonidine patches and clonidine tablets. The comparison of cost was based on the point-of-service adjusted total weighted average cost per day of treatment. As expected, the results of the cost-analysis revealed that clonidine patches were significantly more costly compared to clonidine tablets.

Two different types of pharmacoeconomic analysis could have been performed to determine the cost-effectiveness of the combination antihypertensive agents within this therapeutic class. One alternative was to use cost-minimization to compare the combination antihypertensives to their respective agents given separately solely based on cost. However, this alternative would have neglected to account for the primary potential benefit of combination products, improved patient compliance with medication therapy. Therefore, to account for the potential differences in relative clinical effectiveness, a CEA was performed based on the results of three observational studies examining compliance with combination antihypertensives.

The observational studies included two studies that examined compliance with the combination product amlodipine/benazepril and another study that examined compliance with combination ACE/hydrochlorothiazide (HCTZ) products (enalapril/HCTZ and lisinopril/HCTZ). These studies revealed increased compliance ranging from 7% to 20% with the combination antihypertensives compared to the respective agents given separately. For purposes of the CEA, the increased compliance associated with combination antihypertensive products was assumed to be 10%. To determine the relative cost-effectiveness of the combination products, two simple cost-effectiveness decision models were constructed, one comparing the DHP/ACE combination products (amlodipine/benazepril and felodipine/enalapril) to their respective agents given separately and another comparing the verapamil/ACE combination product (verapamil/trandolapril) to its respective agents given separately. The cost used in the model was the total cost of drug treatment for one-year. The outcome/effect was ‘days of treatment.’

Theoretically, 'days of treatment' is a surrogate indicator of compliance. Likewise, compliance with drug therapy theoretically results in overall improved blood pressure control.

The results from the CEAs are as follows:

- DHP/ACE combination
  - The two agents given separately were more cost-effective compared to Lexxel (felodipine/enalapril) and Lotrel (amlodipine/benazepril). However, the incremental cost-effectiveness ratio was relatively low, indicating that the combination products may be a cost-effective alternative therapy.
- Verapamil/ACE combination
  - The two agents given separately were more cost-effective compared to Tarka (verapamil/trandolapril). For this comparison, the incremental cost-effectiveness ratio was relatively high, indicating that the combination product is not a cost-effective alternative therapy.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of miscellaneous antihypertensive best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations, the Committee agreed that a group of miscellaneous antihypertensive agents that included: clonidine patches and amlodipine/ benazepril best achieved this goal when compared to other combination groups of miscellaneous antihypertensive agents, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 1 absent) to accept the miscellaneous antihypertensive cost-analysis presented by the PEC. The P&T Committee concluded that felodipine/enalapril and verapamil/trandolapril were not cost-effective relative to the other miscellaneous antihypertensive agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the miscellaneous antihypertensive agents, and other relevant factors, the P&T Committee recommended that felodipine/enalapril and verapamil/trandolapril be classified as non-formulary under the UF. The P&T Committee also recommended that clonidine tablets, clonidine patches, amlodipine/ benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted 11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril and verapamil/trandolapril be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

C. Miscellaneous antihypertensive agents Medical Necessity Criteria. The P&T Committee concluded that because the only miscellaneous antihypertensive agents classified as non-formulary under the UF are the combination agents felodipine/enalapril and verapamil/

trandolapril, and because the individual components of both of these agents are available separately on the UF, only two of the five general medical necessity criteria could potentially apply. Therefore, based on the clinical evaluation of felodipine/enalapril and verapamil/ trandolapril and conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the following medical necessity criteria may apply:

1) Use of a formulary pharmaceutical agent is contraindicated, and the use of a non-formulary agent is not contraindicated.

2) The patient previously responded to the non-formulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to accept the miscellaneous medical necessity criteria.

D. Miscellaneous Antihypertensive Agents UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend an implementation period of 60 days.

E. Miscellaneous Antihypertensive Agents Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two miscellaneous antihypertensive agents would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that amlodipine/benazepril, hydralazine and clonidine tablets be added to the BCF.

Conclusion: Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets were recommended for inclusion on the BCF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to include Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets on the BCF

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

A. GABA-Analogs Relative Clinical Effectiveness: The DoD P&T Committee evaluated the relative clinical effectiveness of the GABA-analogs marketed in the US: gabapentin (Neurontin and various generics), pregabalin (Lyrica), and tiagabine (Gabitril). Information regarding the safety, effectiveness, and clinical outcome of these drugs was considered. Although gabapentin, pregabalin, and tiagabine are all FDA indicated as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused primarily on the use of these agents for the treatment of various types of neuropathic pain. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) Efficacy

a) Endpoints: The primary efficacy measure used in the clinical trials was pain experienced by the patients during the previous 24 hours, rated on an 11-point numerical scale (0= no pain; 10= worst possible pain). The primary efficacy parameter was the change in the mean daily pain

score from baseline to the study end; the proportion of patients responding to therapy was a secondary outcome. A >50% reduction in mean pain scores between baseline and study end are considered relevant. Numbers needed to treat (NNT), defined as the number of patients needed to be treated with the drug to result in one patient obtaining a >50% reduction in mean pain score, were then calculated to give a measure of the effect size.

b) Efficacy of GABA analogs for treatment of pain associated with diabetic peripheral neuropathy (DPN):

Place in Therapy: Guidelines from the American Diabetes Association recommend gabapentin and pregabalin and other therapies as initial therapy for the treatment of pain associated with DPN. There is no preference stated for gabapentin or pregabalin in the guidelines. The guidelines do not mention tiagabine.

Clinical Trials for DPN-related pain: There are no head-to-head clinical trials comparing pregabalin with gabapentin for DPN-related pain, and there are no clinical trials evaluating efficacy of tiagabine for this condition. The Committee reviewed the following trials evaluating the use of the GABA-analogs in DPN: one comparative trial of gabapentin vs. amitriptyline; one active controlled trial of pregabalin and amitriptyline vs. placebo; a Cochrane review of four placebo controlled trials with gabapentin; and three placebo controlled trials with pregabalin.

In the comparative trial of gabapentin (900-1800 mg/day) vs. amitriptyline (25-75 mg/day), both treatments resulted in significant reductions in mean pain score from baseline; there was no difference between the two drugs at study endpoint. This trial was limited by small patient enrollment (N=28). In the active controlled trial of pregabalin (600 mg/day) and amitriptyline (75mg/day) vs. placebo, pregabalin did not differ from placebo in the change in mean pain score from baseline or in the proportion of patients achieving at least a 50% decrease in mean pain score at endpoint. These endpoints reached statistical significance when amitriptyline was compared to placebo. Direct comparisons of the efficacy of pregabalin vs. amitriptyline were not conducted in the trial. Overall, treatment with pregabalin 600 mg/d (200 mg three times a day) was no more effective than placebo in the treatment of DPN-related pain in this study.

A Cochrane review of four placebo controlled trials enrolling 281 patients that evaluated the efficacy of gabapentin for DPN pain favored gabapentin [relative risk 2.21 (95% confidence interval 1.65, 2.96)]. The gabapentin doses ranged from 900-3600 mg/day. Overall, 64% of patients improved with gabapentin compared to 28% with placebo. The combined NNT for effectiveness of gabapentin in DPN compared to placebo was 2.9.

The results of the three double-blinded, placebo controlled trials evaluating pregabalin in DPN were reported to the Committee. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Pregabalin in doses of 100 mg three times a day (300 mg/day) and 200 mg three times a day (600 mg/day) resulted in statistically significant improvements in the mean pain score at endpoint and in the proportion of patients obtaining at least a 50% reduction in pain score from baseline compared to placebo. The mean pain score at endpoint was 1.26 to 1.45 points lower with pregabalin (300 mg/day and 600 mg/day doses, respectively) than placebo. The percentage of patients responding to pregabalin 300 mg/day ranged from 40% to 46%; the percentage of responders to pregabalin 600 mg/day ranged from 39% to 48%, while the placebo responder rate was 15%. Although 600 mg/day was evaluated in these trials, the product labeling for pregabalin does not recommend doses above 300 mg/day for DPN, as doses of 600 mg/day do not provide greater

benefit. The NNT with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.4 to 4.0 for the three studies.

DPN Conclusion: Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNT, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with DPN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to DPN.

c) Efficacy of GABA analogs for treatment of pain associated with post-herpetic neuralgia (PHN):

Place in therapy: Practice guidelines endorsed by the American Academy of Neurology for the treatment of pain in patients with PHN give a Level A, class I recommendation (strongest evidence for efficacy) to gabapentin and pregabalin. First-line options for the treatment of PHN included gabapentin, pregabalin, lidocaine patch, tricyclic antidepressants and controlled release morphine or oxycodone. The guideline does not give a preference to either pregabalin or gabapentin for the treatment of PHN-related pain, and does not mention tiagabine.

Clinical Trials for PHN pain: There are no head to head clinical trials comparing pregabalin with gabapentin for treatment of pain in patients with PHN. There are no trials evaluating efficacy of tiagabine for PHN-related pain. The Committee evaluated two placebo controlled trials with gabapentin, and three placebo controlled trials with pregabalin for this pain syndrome.

Two double-blind placebo controlled trials compared gabapentin vs. placebo for the treatment of pain associated with PHN. Gabapentin doses ranging from 600 mg three times a day to 900 mg three times a day were evaluated in the two trials. In both trials, patients receiving gabapentin had a statistically significant reduction in mean daily pain score at study end, compared to placebo. The mean pain score at endpoint was 2.1 points lower with gabapentin (all doses) than placebo. In the first trial, 43% of patients receiving gabapentin 900 mg three times a day rated their pain as much improved vs. 12.1% with placebo. In the second trial, the responder rate was 14% with placebo, 32% with gabapentin 600 mg three times a day and 34% with gabapentin 800 mg three times a day.

A Cochrane review of the two placebo controlled trials discussed earlier (enrolling 563 patients) that evaluated the efficacy of gabapentin for PHN pain favored gabapentin [relative risk 2.50 (95% confidence interval 1.80, 3.48)]. Overall, 43% of patients improved with gabapentin compared to 17% with placebo. The combined NNT from these two studies for effectiveness compared to placebo was 2.9.

Three double-blind placebo controlled trials evaluated pregabalin for the treatment of pain associated with PHN. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Twice a day dosing of pregabalin was used in one trial, while a three times a day regimen was used in the remaining two trials; doses ranged from 150 mg/day to 600mg/day. All pregabalin doses resulted in significant reductions in mean pain scores compared to placebo. The mean pain score at endpoint was 0.88 to 1.79 points lower with pregabalin (all doses) than placebo. The percentage of patients responding to pregabalin 150 mg/day ranged from 26% to 27%, the percentage of responders to pregabalin 300 mg/day ranged from 27% to 28%, the percentage of responders to pregabalin 600 mg/day ranged from 38% to50%, while the placebo responder rate ranged from 8% to 10%.

The NNT with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.3 to 6.3 in the three studies, depending on the dose of pregabalin.

PHN Conclusion: Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with PHN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to PHN.

d) Efficacy of GABA analogs for other neuropathic pain syndromes:

Clinical Trials: The P&T Committee evaluated two trials assessing the efficacy of gabapentin, and one trial assessing the efficacy of tiagabine in other types of neuropathic pain syndromes. Gabapentin was evaluated in doses up to 2.4 g/day in 305 patients with a variety of different types of neuropathic pain syndromes, including complex regional pain syndrome, PHN, radiculopathy, and post laminectomy. The authors reported there was an overall significant difference in mean pain score favoring gabapentin over placebo, however there was no significant difference between gabapentin and placebo at weeks 7 and 8 (the differences at weeks 1,3,5,6 were significant). When gabapentin was compared to placebo in 19 patients with post-amputation limb pain, gabapentin was significantly better than placebo at study endpoint. The effect of tiagabine in painful neuropathy was studied in a 4-week, open-label, non-placebo-controlled pilot trial in 17 adults. Overall pain indices tended to decline, but results did not reach statistical significance for tiagabine vs. placebo, given the high and dropout rate (only 8 patients completed the study).

Other Neuropathic Pain Syndromes Conclusions: The Committee concluded that gabapentin demonstrated modest clinical efficacy for other neuropathic pain syndromes, based on two placebo controlled trials. No conclusion can be made concerning the efficacy of tiagabine for neuropathic pain due to limited evidence (one poorly designed study and overall lack of trials evaluating the efficacy of tiagabine for neuropathic pain). Pregabalin has not been evaluated in other types of neuropathic pain syndromes.

e) Efficacy of GABA Analogs for Treatment of Partial Seizures:

Place in Therapy: A report endorsed by the American Academy of Neurology and the American Epilepsy Society assigned both gabapentin and tiagabine Level A recommendations (highest recommendation) as adjunctive therapy for partial seizures. There was no mention of pregabalin due to publication of the guideline prior to FDA approval.

Clinical Trials: Gabapentin, pregabalin, and tiagabine have all been evaluated in the adjunctive treatment of epilepsy in placebo controlled trials. There are no head to head trials comparing efficacy of one GABA-analog to another in seizure disorders. The results of one meta-analysis conducted with gabapentin and tiagabine, and three double-blinded placebo controlled trials with pregabalin support efficacy of all three agents in patients with epilepsy, based on the endpoint of 50% reduction in seizure frequency.

Partial Seizures Conclusions: The committee concluded that gabapentin, pregabalin, and tiagabine demonstrate clinical efficacy for adjunctive treatment of partial seizures. Since the GABA analogs are added onto regimens comprised of other antiepileptic drugs, there is no evidence to suggest clinical superiority of any GABA agent over another.

Overall efficacy conclusion: The Committee concluded that there is no evidence of superiority of either gabapentin or pregabalin for treatment of pain associated with DPN or PHN. Efficacy of gabapentin for other types of neuropathic pain syndromes appears modest, but there is no efficacy evidence for pregabalin in other types of neuropathic pain. There is insufficient evidence to make conclusions regarding the efficacy of tiagabine in DPN, PHN, or other types of neuropathic pain syndromes.

2) Safety and Tolerability: The Committee assessed the comparative safety and tolerability of gabapentin, pregabalin, and tiagabine including rare but serious adverse effects, common adverse effects, potential for drug interactions, and safety of use in special populations.

Serious Adverse Effects:
All three GABA analogs (gabapentin, pregabalin, and tiagabine) should be gradually tapered when therapy is discontinued, to minimize the potential for increased seizure frequency. Post-marketing reports have linked tiagabine with new onset seizures and status epilepticus in patients who did not have epilepsy. There are reports of sudden unexplained death in patients with epilepsy taking gabapentin or tiagabine, however, it is unknown whether the unexplained deaths were a direct result of gabapentin or tiagabine therapy. Tiagabine has been associated with cognitive/neuropsychiatric events such as impaired concentration, speech and language problems, confusion and fatigue. Pregabalin has been associated with creatine kinase elevations and three reports of rhabdomyolysis in premarketing clinical trials.

Common Adverse effects:
The most commonly reported side effects associated with gabapentin, pregabalin and tiagabine include dizziness, somnolence, and asthenia. These adverse effects appear to be dose related, and tend to decrease over time. Based on clinical trial experience, tiagabine appears more commonly associated with nervousness and tremor, while gabapentin and pregabalin are associated the weight gain, dizziness, somnolence and peripheral edema.

Due to differences in study design for the placebo controlled trials and the lack head to head trials, comparisons of adverse event rates between the GABA analogs are difficult. In general, clinical trials using flexible dosing regimens and slow titration schedules result in fewer patients dropping out of the trial and lower adverse event rates than trials incorporating fixed dosing regimens and quick titration schedules.

A comparison of the product labeling for all three GABA analogs lists the following adverse events, which have been placebo-adjusted. Peripheral edema: 8.3% with gabapentin, and 9% with pregabalin; an incidence is not provided in the tiagabine package insert. Dizziness: 28% with gabapentin, 21% with pregabalin, and 27% with tiagabine. Somnolence: 21.4% with gabapentin, 12% with pregabalin, and 12% with tiagabine.

Numbers needed to harm (NNH) is another way of measuring adverse events and for the purpose of this review was defined as any adverse effect leading to patient withdrawal from a study. NNH could be calculated for two of the trials assessing pain in PHN. For gabapentin, the NNH was 11.2; for pregabalin, the NNH was 3.7. Although the NNH is smaller with pregabalin, possibly indicating a less tolerable drug, the titration period with pregabalin was more rapid (over 1 week) compared to the gabapentin trial (over 4 weeks). A longer titration period may have led to a more favorable NNH in the gabapentin trial. When the NNHs were calculated from a clinical trial evaluating pregabalin for treatment of DPN and PHN in both fixed and flexible doses, the NNH was 10.7 with the flexible dosing regimen, and 5.8 with the fixed dosing regimen. The flexible dosing regimen incorporated a longer titration schedule than

with the fixed dose, which could possibly account for the more favorable NNH with the flexible dosing.

Drug Interactions:

Gabapentin and pregabalin are not metabolized by hepatic CYP450 enzymes, thus are not associated with significant drug interactions. Tiagabine is primarily metabolized by CYP450 and is highly protein bound, thus drug interactions have been reported with concomitant usage with other anticonvulsant drugs (carbamazepine, phenytoin, phenobarbital, primidone).

Special populations:
Renal Impairment: Gabapentin and pregabalin are both renally eliminated, and both drugs require dosage reductions with decreasing renal function. Reductions in gabapentin and pregabalin dosages may be required in patients who have age related compromised renal function.

Hepatic Impairment: Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine or a longer dosing interval compared to patients with normal hepatic function.

Pregnancy: All three GABA analogs are rated as pregnancy category C, and should be used during pregnancy only if the potential benefit justifies the potential risk.

Overall Safety and Tolerability Conclusion: The Committee concluded withdrawal seizures occurring with sudden discontinuation of therapy have been reported with all three GABA analogs. Tiagabine is associated with serious adverse events, including neuropsychiatric and cognitive effects and development of seizures in patients who did not previously have epilepsy. Dizziness and somnolence are the most commonly reported adverse effects with pregabalin and gabapentin, while tremors and nervousness are more commonly reported with tiagabine. Indirect comparisons, based on NNH and the percentage of patients discontinuing therapy due to adverse effects, show only minor differences in tolerability between gabapentin and pregabalin. Tiagabine has a greater drug interaction potential compared to gabapentin and pregabalin, due to hepatic metabolism. Both gabapentin and pregabalin require dose adjustment in patients with renal dysfunction.

3) Other Factors:
FDA Approved indications: Gabapentin and pregabalin are both FDA-approved for treating pain associated with PHN. Pregabalin is the sole agent in the class approved for treating pain associated with DPN, however, controlled clinical trial data support the efficacy of gabapentin. Gabapentin, pregabalin, and tiagabine are all approved as adjunctive therapy in seizure disorders.

Controlled Substance Class: Pregabalin is the only GABA-analog that is a schedule V controlled substance. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms of insomnia, nausea, headache, or diarrhea, suggestive of dependence. Due to the schedule V status, no more than 5 refills can be obtained in a 6-month period.

Use in Pediatrics: Gabapentin is approved in for use as an anticonvulsant in patients as young as three years old. Tiagabine is approved for use in patients as young as 12 years old for treatment of epilepsy. Pregabalin has not been studied in pediatric patients.

Pharmacokinetics: Gabapentin exhibits non-linear pharmacokinetics; as the dose of gabapentin is increased, bioavailability decreases. In contrast, pregabalin exhibits linear pharmacokinetics, and the oral bioavailability of pregabalin is > 90% independent of dose. However, a linear dose response has not resulted in significantly improved pain relief with pregabalin administered at higher doses (600mg/d) vs. lower doses (300 mg/d). In fact, the manufacturer of pregabalin does not recommend greater than 300 mg/d for DPN because 600 mg/d pregabalin has not been proven to significantly improve pain scores compared to 300 mg/d, and greater than 600 mg/d for PHN.

Frequency of Dosing and Titration Schedules: Pregabalin can be dosed twice daily for treatment of pain associated with PHN, while gabapentin requires three times a day dosing. For pain associated with DPN, both pregabalin and gabapentin require three times a day dosing. Twice a day dosing of pregabalin in DPN-related pain is not recommended by the manufacturer, as twice daily dosing did not show significant differences in efficacy as compared to placebo in unpublished trials available from the FDA. The dosage initiation schedule for pregabalin is less complex and requires a shorter time period than the dosage titration recommended with gabapentin. Statistical improvements in mean pain score in clinical trials have occurred within 1-2 weeks of initiation of both gabapentin pregabalin therapy.

Provider Opinion: A survey of DoD providers ranked gabapentin first in terms of clinical efficacy for neuropathic pain, due to more personal clinical experience, compared to tiagabine and pregabalin. Pregabalin was ranked second in terms of clinical efficacy, primarily due to lack of clinical experience, but providers did prefer ease of titration and twice daily dosing in PHN. The majority of providers' therapeutic strategy would include a trial of gabapentin first, followed by pregabalin if therapy with gabapentin was not successful. Tiagabine was rarely used in neuropathic pain, and if chosen, it was preferred as adjunctive therapy to other treatments for neuropathic pain, not as an alternative to gabapentin or pregabalin. All three drugs (gabapentin, pregabalin, and tiagabine) were considered therapeutically interchangeable for use in patients with partial seizures.

Other Factors Conclusions: The Committee concluded that pregabalin is the only GABA-analog that has restrictions in prescribing due to its controlled status. The linear pharmacokinetic profile of pregabalin has not resulted in significant improvement in efficacy with higher doses. Pregabalin may potentially have improved patient compliance compared to gabapentin, due to an easier titration schedule and twice a day dosing in patients with PHN. However, three times a day dosing is recommended for pregabalin in patients with DPN. There is no published data evaluating the efficacy of pregabalin in pediatrics.

Overall Clinical Effectiveness Conclusion: The Committee concluded that (1) the efficacy of gabapentin and pregabalin for treating pain associated with either DPN or PHN appears similar; (2) gabapentin is the only GABA-analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for the use an adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status.

Overall the Committee agreed that based on clinical usefulness alone, there is no basis for classifying any of the GABA-analog as non-formulary.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 1 abstain, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. Relative CEA: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). A CEA was used to determine the relative cost-effectiveness of agents within the GABA-analog therapeutic class. A Monte Carlo simulation was performed using data from three well designed randomized controlled trials of pregabalin and gabapentin in diabetic peripheral neuropathy and post-herpetic neuralgia. Flexible dose (average 378 mg) and fixed dose (600 mg) pregabalin were compared to daily gabapentin doses of 600, 900, 1200, 1800 and 2400 mg. Costs used in the model were the total weighted average cost per day of treatment across all points of service in the MHS. The principal outcome of interest was the mean reduction in weekly pain scores at the 12th week.

Results of the CEA showed gabapentin at doses of up to 2400 mg to be the most cost effective GABA-analog drug in the treatment of neuropathic pain with the lowest average cost per patient over twelve weeks of treatment, and no clinically significant differences in outcomes.

The results of the above analyses were then incorporated into a BIA, which accounted for other factors and costs associated with a potential decision regarding formulary status of GABA-analog drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the BIA further confirmed the results of the CEA. Gabapentin was found to be the most cost-effective GABA-analog drug overall in the treatment of neuropathic pain.

Conclusion: The P&T Committee concluded that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain. The cost-effectiveness of tiagabine was also considered, and it was determined that nothing would be gained clinically or economically by making tiagabine non-formulary.

COMMITTEE ACTION: The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) with the relative CEA of the GABA-analog drugs presented.

Based on the results of the two analyses, the P&T Committee concluded that pregabalin was much more costly, and had similar relative clinical effectiveness compared to gabapentin in both neuropathic pain and partial seizures. Tiagabine also had similar relative clinical effectiveness in partial seizures as compared to gabapentin and pregabalin. However, due to its low utilization, and small, static market share, it was felt that tiagabine contributed minimally to the amount spent in this drug class. Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF.

C. GABA analogs UF Medical Necessity Criteria: Based on the clinical evaluation of the GABA analogs and conditions for establishing medical necessity for a non-formulary

medication provided in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of formulary agents is contraindicated, and the use of pregabalin is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary agents, and the patient is expected to tolerate pregabalin.

3) Treatment with formulary agents has resulted in a therapeutic failure, and the patient is expected to respond to pregabalin.

4) The patient previously responded to the pregabalin and changing to a formulary agent would incur an unacceptable clinical risk.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 1 opposed, 0 abstained, 2 absent) to accept the GABA-analog medical necessity criteria.

D. GABA-analog UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend an implementation period of 60 days.

E. GABA-analog BCF Review and Recommendations: The P&T Committee reviewed the GABA analogs recommended for inclusion on the UF to select the BCF GABA analog.

Gabapentin is currently included on the BCF. From a clinical and economic standpoint, all strengths and formulations of gabapentin are rational selections for the BCF. Gabapentin is the highest utilized GABA-analog in all three points of service (MTF, TRRx, and TMOP), is efficacious in treating a variety of neuropathic pain syndromes, and is now generically available.

Conclusion: The Committee concurred with the recommendations to place all formulations and strengths of gabapentin on the BCF.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to maintain all formulations and strengths of gabapentin on the BCF.

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

10. ADJOURNMENT

The third day of the meeting adjourned at 1130 hours on February 16, 2006. The dates of the next meeting are May 9 – 11, 2006.

_____//signed//_____
Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 06	OABs	tolterodine IR (Detrol) oxybutynin patch (Oxytrol) trospium (Sanctura)	BCF	oxybutynin IR (Ditropan tabs/soln) tolterodine SR (Detrol LA)	Pending approval	Pending approval	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	Pending approval	Pending approval	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	Pending approval	Pending approval	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs February 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Deferasirox (Exjade; Novartis) tablets for oral suspension; iron chelator	Nov 05; treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years and older	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Sorafenib (Nexavar) tablets; multi-kinase inhibitor	Dec 05 (priority review); treatment of patients with advanced renal cell carcinoma	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed. Quantity limits recommended: TMOP: 180 tablets per 45 days (if the product becomes available in this point of service; Retail Network: 120 tablets per 30 days

Appendix C – Table 3. Table of Abbreviations

ACE	angiotensin converting enzyme
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BP	blood pressure
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
DHP	dihydropyridine
DM	diabetes mellitus
DoD	Department of Defense
DPN	diabetic peripheral neuropathy
ECF	Extended Core Formulary
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
HCTZ	hydrochlorothiazide
JNC VII	Joint National Commission VII
MHS	Military Health System
MTF	military treatment facility
NNH	number needed to harm
NNT	number needed to treat
OAB	overactive bladder
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PHN	post-herpetic neuralgia
SBP	systolic blood pressure
SUI	stress urinary incontinence
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary

17 November 2005

DECISION PAPER:

NOVEMBER 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes: Four committee vote counts were incorrectly recorded in the minutes of August 2005 DoD Pharmacy and Therapeutics (P&T) meeting. Corrections are as follows:

1) Item 8a. T*he P&T Committee concluded that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (15 for, 0 against, 1 abstained, 1 absent)

2) Item 9a: *The P&T Committee voted to accept the clinical effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

3) Item 9b: *The P&T Committee voted to accept the cost effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (17 for, 0 against, 0 abstained, 0 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

4) Item 9c: *The P&T Committee voted to accept the medical necessity criteria for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

5. ITEMS FOR INFORMATION

6. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on six new agents that had been approved by the FDA, of which five have been introduced to the U.S. market since the August 2005 meeting. None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee did review one new drug for quantity limits. Mometasone furoate oral inhaler is a new corticosteroid for asthma that has a unique deliver device (Asmanex Twisthaler 220 mcg). The device delivers 200 mcg per actuation, and is available in several sizes providing 14 inhalations (for institutional use), 30 inhalations, 60 inhalations (for patients requiring 1 dose/day) or 120 inhalations (for patients requiring more than 1 dose/day). There are quantity limits for the other inhaled corticosteroids; therefore, quantity limits for Asmanex Twisthaler are recommended.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend that mometasone furoate oral inhaler 220 mcg (Asmanex Twisthaler) have

quantity limits of 120 inhalations per 30-days (retail pharmacy network), or 360 inhalations per 90-days (TRICARE Mail Order Pharmacy (TMOP)), consistent with the limits imposed with other inhaled corticosteroids (see paragraph 6 on page 14 of P&T Committee minutes for rationale and summary of PA criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

7. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MECASERMIN (INCRELEX) INJECTION

The Committee agreed that a PA was needed for mecasermin (Increlex) subcutaneous injection due to potential confusion with other growth products and misuse potential.

***COMMITTEE ACTION*:** Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that PA be required for mecasermin (see paragraph 7 on pages 14 – 15 of P&T Committee minutes for rationale and summary of PA criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

***COMMITTEE ACTION*:** The Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that the PA for mecasermin should have an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA) (see paragraph 7 on page 15 of P&T Committee minutes).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

8. QUANTITY LIMITS

A. Etanercept (Enbrel) – Etanercept was initially approved as a 25 mg twice-weekly injection for the treatment of RA and was available only as a 25-mg vial in sealed packages containing 4 vials (2 weeks supply for RA, psoriatic arthritis, or ankylosing spondylitis or 1-2 weeks supply for psoriasis). Dosing recommendations for etanercept have changed to allow weekly dosing for all indications, and etanercept recently became available as a 50 mg/mL pre-filled syringe, which is now the preferred method of dosing. The current days supply limit of a 4-week supply in retail, a 6-week supply in the TMOP program, and up to a 6-week supply at military treatment facilities (MTFs) (based on instructions for use on the prescription) is

problematic for the 50 mg/mL pre-filled syringes, which are supplied in sealed packages containing 4 syringes.

The Committee agreed that, given the cost of etanercept and the existence of similar quantity limits for other biologics for the treatment of RA and/or psoriasis, a day's supply limit should be retained, but adjusted to 8 weeks supply in mail order and MTFs to allow for dispensing of whole packages.

***COMMITTEE ACTION*.** The Committee voted (16 for, 0 opposed, 2 abstained, 1 absent) to recommend changing the quantity limits for etanercept (Enbrel) subcutaneous injection to a four-week supply in retail, an eight-week supply in the TMOP program, and up to an eight-week supply at MTFs, based on instructions for use on the prescription (see paragraph 8A on pages 15 – 16 of P&T Committee minutes for rationale and summary of quantity limits).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. Zolmitriptan (Zomig) – The current quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) is 8 tablets per 30 days or 24 tablets per 90 days. Currently, zolmitriptan tablets are available in blister packs of 3 or 6 tablets. The current quantity limit for zolmitriptan nasal spray, which is packaged in boxes of 6 unit-dose nasal spray units, is 12 unit-doses per 30 days or 36 unit-doses per 90 days. The Committee agreed that the quantity unit for zolmitriptan tablets should be increased to be consistent with the quantity limit for the nasal spray and to allow for dispensing of whole packages of zolmitriptan tablets.

***COMMITTEE ACTION*.** The Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend changing the quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) to 12 tablets per 30 days or 36 tablets per 90 days (see paragraph 8B on page 16 of P&T Committee minutes for rationale and summary of quantity limits).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

9. ALZHEIMER'S DRUG CLASS REVIEW. ACETYLCHOLINESTERASE INHIBITOR AND N-METHYL D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the acetylcholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne), and tacrine (Cognex), and the NMDA receptor antagonist memantine (Namenda) used to treat the cognitive symptoms of Alzheimer's disease. Together these drugs account for approximately $65M annually in Military Health System (MHS) drug class expenditures.

A. COMMITTEE ACTION: The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that for the purposes of the UF clinical review, with the exception of tacrine, none of the acetylcholinesterase inhibitors have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other acetylcholinesterase inhibitors; and that memantine has a place in therapy due to its indication for treatment of dementia in moderate to severe Alzheimer's disease. The P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause hepatic injury.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the acetylcholinesterase inhibitors and memantine, and other relevant factors, the P&T committee recommended (10 for, 6 against, 2 abstained, 1 absent) that tacrine be classified as non-formulary under the UF, with memantine, donepezil, rivastigmine, and galantamine remaining on the UF (see paragraphs 9A – B on pages 16 – 20 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of tacrine and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) medical necessity criteria for tacrine. (See paragraph 9C on page 20 of P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9D on page 20 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend donepezil as the Extended Core Formulary agent (see paragraph 9E on pages 20 – 21 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

10. NASAL CORTICOSTEROIDS FOR ALLERGIC RHINITIS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the nasal corticosteroids used to treat allergic rhinitis. Six agents were considered in the review, beclomethasone dipropionate (Beconase AQ, Vancenase AQ, and Vancenase AQ DS), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone propionate (Flonase), mometasone furoate (Nasonex), and triamcinolone acetonide (Nasacort AQ). The nasal corticosteroids rank in the top 20 in terms of MHS drug class expenditures at $60.2M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that no one nasal corticosteroid has a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other nasal corticosteroids.

The cost analysis showed that flunisolide, fluticasone propionate, and mometasone furoate are more cost effective than the other nasal corticosteroids. The budget impact analysis also concluded that flunisolide, fluticasone propionate, and mometasone furoate represent the best value to DoD.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the nasal corticosteroids, and other relevant factors, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent), that beclomethasone dipropionate (Beconase AQ, Vancenase AQ, Vancenase AQ DS), budesonide (Rhinocort AQ), and triamcinolone acetonide (Nasacort AQ) be classified as non-formulary under the UF, and that flunisolide (Nasarel), fluticasone propionate (Flonase), and mometasone furoate (Nasonex) be classified as formulary under the UF (see paragraphs 10A – B on pages 21 – 25 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of beclomethasone dipropionate, budesonide, and triamcinolone acetonide and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) medical necessity criteria

for the nasal corticosteroids. (See paragraph 10C on page 25 of P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 10D on page 25 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend fluticasone propionate as the Basic Core Formulary (BCF) agent (see paragraph 10E on page 25 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

11. ANTIDEPRESSANTS GROUP 1 (AD1) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the antidepressant medications, with the exception of the monoamine oxidase inhibitors and tricyclic antidepressants. The AD1s accounted for $290 million in MHS expenditures in FY05. Individual agents in the AD1 drug class are listed below.

- *Selective Serotonin Reuptake Inhibitors (SSRIs)* – citalopram (generics, Celexa); escitalopram (Lexapro); fluoxetine (generics, Prozac); fluoxetine 90-mg delayed release capsules (Prozac Weekly); fluoxetine in special packaging for the treatment of premenstrual dysphoric disorder (PMDD) (Sarafem); fluvoxamine (generics); paroxetine immediate release (generics, Paxil, Pexeva); paroxetine controlled release (Paxil CR); and sertraline (Zoloft)
- *Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)* - venlafaxine (Effexor, Effexor XR); duloxetine (Cymbalta)

- *Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)* - bupropion immediate and sustained release (generics, Wellbutrin, Wellbutrin SR); bupropion extended release (Wellbutrin XL)
- *Alpha-2 antagonists* – mirtazapine (generics, Remeron)
- *Serotonin modulators* – nefazodone (generics); trazodone (generics, Desyrel)

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that: 1) the AD1s offer similar efficacy in treating major depressive disorder (MDD) with the exception of limited data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram; 2) FDA approval of fluoxetine for MDD in children, and broad usefulness of paroxetine and sertraline in psychiatric conditions other than MDD were considered clinical advantages; 3) with the exception of venlafaxine, where nausea is a greater problem, there are little data to support a substantial difference among AD1s with respect to patient tolerability; however, adverse effect profiles do differ across AD1s; 4) bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs; 5) fluvoxamine, fluoxetine, paroxetine and duloxetine have a higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine; 6) the likelihood of discontinuation syndrome with the SSRIs corresponds with half-life (shortest half-life = greatest risk). fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine, and venlafaxine may be associated with more discontinuation symptoms than SSRIs; while discontinuation symptoms appear rare with bupropion; 7) rare but serious adverse effects are associated with duloxetine (recent case reports of hepatotoxicity), bupropion (seizure), nefazodone (hepatotoxicity), mirtazapine (agranulocytosis), and trazodone (priapism); and 8) drugs of concern in specific patient populations include duloxetine (hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk).

Relative Cost Effectiveness Analysis: Differences in efficacy, safety, and tolerability among the AD1s were incorporated into two separate cost effectiveness analyses (CEAs). The first CEA was based on the results obtained via a multi-attribute utility theory (MAUT) analysis, which included differences between agents in clinical outcome, evidence and/or FDA-approved indications supporting use for psychiatric and non-psychiatric conditions other than MDD, such as generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), diabetic peripheral neuropathic pain (DPNP), as well as usefulness in the pediatric population, and safety/tolerability factors such as risk of drug interactions, use in pregnancy, contraindications, potential for rare but serious adverse events, and risk of sexual dysfunction. The second CEA (CEA-Response) was based on findings reported in the DoD Pharmacoeconomic Center's clinical review and the Oregon Health & Science University's Drug Class Review on Second Generation Antidepressants as part of the Drug Effectiveness Review Project. This CEA assessed the costs and outcomes of treatment for MDD during the acute phase of treatment.

Based on the results of the two analyses, the P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that: 1) fluoxetine 90-mg delayed release capsules (Prozac Weekly) and fluoxetine in special packaging for treatment of PMDD (Sarafem) were greater than seven-fold more costly, and had similar relative clinical effectiveness compared to generic fluoxetine; 2)

sertraline had equal (CEA-Response) or slightly greater (CEA-MAUT) relative clinical effectiveness, but was significantly more costly compared to fluoxetine (however, sertraline is projected to go generic in June 2006); 3) escitalopram was shown to have lower overall relative clinical effectiveness (CEA-MAUT) compared to fluoxetine, but potentially greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to citalopram; however, at a significantly greater cost; 4) the CEA-MAUT and CEA-Response both showed that paroxetine and paroxetine CR had similar relative clinical effectiveness, but paroxetine CR was significantly more costly compared to paroxetine; 5) venlafaxine was shown to have greater overall relative clinical effectiveness (CEA-MAUT) and greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to duloxetine for a similar cost; and 6) bupropion XL was shown to have greater overall relative clinical effectiveness (CEA-MAUT) but similar relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to bupropion SR at a significantly greater cost.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the antidepressants, and other relevant factors, the P&T Committee recommended (12 for, 5 against, 1 abstained, 1 absent) that escitalopram (Lexapro), fluoxetine 90-mg delayed release capsules (Prozac Weekly), fluoxetine in special packaging for PMDD (Sarafem), paroxetine controlled release (Paxil CR), duloxetine (Cymbalta), and bupropion extended release (Wellbutrin XL) be classified as non-formulary under the UF, with citalopram, fluoxetine, fluvoxamine, paroxetine immediate release, sertraline, venlafaxine, venlafaxine extended release, nefazodone, trazodone, bupropion immediate and sustained release, and mirtazapine remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued. (See paragraphs 11 A – B on pages 26 – 40 of the P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of the AD1s and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 against, 1 abstained, 2 absent) medical necessity criteria for escitalopram (Lexapro), fluoxetine 90-mg delayed release capsules (Prozac Weekly), fluoxetine in special packaging for PMDD (Sarafem), paroxetine controlled release (Paxil CR), duloxetine (Cymbalta), and bupropion extended release (Wellbutrin XL). (See paragraph 11C on pages 40 – 41 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving non-formulary AD1s, and the need to carefully assess and monitor patients taking this class of medication, the P&T Committee recommended (16 for, 0 against, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 11D on page 41 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend fluoxetine (excluding Prozac Weekly and Sarafem, which are non-formulary), citalopram, sertraline, trazodone, and bupropion sustained release as the BCF agents (see paragraph 11E on pages 41 – 42 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

12. ORAL MACROLIDE/KETOLIDE DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the macrolide/ketolide class of antibiotics. All forms of oral erythromycin (salts and base) were considered in addition to the oral forms of azithromycin, clarithromycin, and telithromycin. Zmax, a 2-gram extended release suspension form of azithromycin was also considered, but was evaluated separately from the other forms of azithromycin. The macrolide/ketolide class of antibiotics ranks 31st in terms of MHS drug class expenditures at $40.7M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that although the macrolide/ketolide agents have significant overlapping antimicrobial activity within the class and with agents in other antibiotic classes, there are some minor differences in terms of safety, effectiveness, and clinical outcomes between the agents. Advantages of a good safety profile, ease of dosing, provider acceptability, and generic availability made azithromycin stand out as a preferred agent in this class. Erythromycin also stood out as a preferred agent in this class due to its many FDA indications, safety, generic availability and familiarity among providers.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the macrolide/ketolide class of antibiotics, and other relevant factors, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that Zmax and telithromycin be classified as non-formulary under the UF, with all oral forms of azithromycin (except Zmax), all forms of clarithromycin, and all oral forms of erythromycin

remaining on the UF (see paragraphs 12 A – B on pages 42 – 48 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of telithromycin and the Zmax formulation of azithromycin and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) medical necessity criteria for Zmax and telithromycin (see paragraph 12C on pages 48 – 49 of P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because of the acute nature of this class of medications and the relatively low number of beneficiaries that would be affected by this formulary action, the P&T Committee recommended (16 for, 1 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 12D on page 49 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend azithromycin 250mg tablets and at least one form of oral erythromycin base or salt (with selection left to each MTF) as the BCF agents (see paragraph 12E on page 49 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

13. ANTI-MUSCARINIC OVERACTIVE BLADDER MEDICATIONS

Portions of the clinical review were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Both the clinical and economic analyses will be completed during the February 2006 meeting; no action necessary.

APPENDIX A – TABLE 1. Implementation Status of UF Decisions

APPENDIX B – TABLE 2. Newly Approved Drugs

APPENDIX C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____// signed //_____
William Winkenwerder, Jr., M.D.
Date: January 19, 2005

Department of Defense
Pharmacy and Therapeutics Committee Minutes

17 November 2005

1. CONVENING

The DoD Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 15 November 2005 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CDR Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Maj Charlene Reith, BSC	Air Force, Pharmacy Officer
LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LTC Don DeGroff, MS	Contracting Officer Representative, TMOP

C. Non-Voting Members Present

Lynn T. Burleson	Assistant General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

COL Kent Maneval, MS, USA	Defense Medical Standardization Board

E. Others Present

Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Dan Remund	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
Debbie Khachikian	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – Four committee vote counts were incorrectly recorded in the minutes of the August 2005 DoD P&T meeting. Corrections are as follows:

1) Item 8a. T*he P&T Committee concluded that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (15 for, 0 against, 1 abstained, 1 absent)
2) Item 9a: *The P&T Committee voted to accept the clinical effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
3) Item 9b: *The P&T Committee voted to accept the cost effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (17 for, 0 against, 0 abstained, 0 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
4) Item 9c: *The P&T Committee voted to accept the medical necessity criteria for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

B. August minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the August 2005 DoD P&T Committee on 13 October 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. CAPT Buss reported TRICARE Management Activity (TMA) funds in support of travel and lodging for DoD P&T members to attend quarterly meetings have been approved.

5. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing: LtCol Bennett briefed the members of the DoD P&T committee regarding the 28 September 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions: PEC staff and TMA briefed the members of the Committee on the implementation status of UF decisions arising from the February, May and August 2005 meetings (see Table 1, Appendix A). The Committee noted that the five drug classes reviewed at the 2005 February and May meetings represent 17% of total Military Health System (MHS) drug spend dollars. These five drug classes plus the four drug classes covered by existing pharmaceutical contracts represent 35% of all MHS drug spend dollars.

6. REVIEW OF RECENTLY-APPROVED AGENTS

The PEC presented clinical information on six new medications approved by the U.S. Food and Drug Administration (FDA). All of the products have been introduced to the U.S. market, with the exception of mecasermin injection (Increlex). (See Table 2, Appendix B). All six medications fall into drug classes not yet reviewed by the DoD P&T Committee; therefore, UF consideration of these products was deferred until drug class reviews are completed.

One of the medications, mometasone furoate oral inhaler (Asmanex Twisthaler), is included as a part of the inhaled corticosteroids drug class, for which there are existing quantity limits. Asmanex Twisthaler provides 200 mcg of mometasone furoate per inhalation, and is available in several sizes, including 14 inhalations (for institutional use), 30 inhalations, 60 inhalations (for patients requiring 1 dose/day) or 120 inhalations (for patients requiring more than 1 dose/day).

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend that mometasone furoate oral inhaler 220 mcg (Asmanex Twisthaler) have quantity limits of 120 inhalations per 30-days (TRICARE Retail Pharmacy (TRRx) Network), or 360 inhalations per 90-days (TRICARE Mail Order Pharmacy (TMOP) program), consistent with the limits imposed with other inhaled corticosteroids.

7. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MECASERMIN (INCRELEX) INJECTION

Mecasermin is used for the long-term treatment of growth failure in children with severe primary insulin-like growth factor (IGF)-1 deficiency (primary IGFD) or with growth hormone (GH) gene deletion that have developed neutralizing antibodies to GH. Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; these patients are not GH deficient, and therefore cannot be expected to respond adequately to exogenous GH treatment. Mecasermin presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for misuse, and monitoring for possible low blood glucose levels (hypoglycemia), because it has insulin-like hypoglycemic effects. Labeling for mecasermin includes specific recommendations for patient selection. Mecasermin should only be used by patients who have the clinical diagnosis of

severe Primary IGFD and are receiving care from appropriate providers (e.g., pediatric endocrinologist/ nephrologist) on a regular basis. Patients using mecasermin must understand how to adjust mecasermin, and be able to recognize hypoglycemia. Mecasermin is not indicated for use in patients with closed epiphyses (bone growth plates).

***COMMITTEE ACTION*:** Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a PA be required for mecasermin (17 for, 0 against, 1 abstained, 1 absent). The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (17 for, 0 against, 1 abstained, 1 absent). PA approvals would be valid for one year.

Coverage is provided for the use of mecasermin as treatment in severe Primary IGFD and in patients who meet all of the following criteria:

- Height standard deviation score $\leq$ -3 and
- Basal IGF-1 standard deviation score $\leq$ -3 and
- Normal or elevated GH
- Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders.
- Thyroid and nutritional deficiencies corrected before initiating mecasermin treatment.
- Have been educated on monitoring and management of hypoglycemia.

Coverage is not provided for patients who:

- Have closed epiphyses (bone growth plates are closed).
- Have active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops).
- Have other cases of growth failure (secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids).

8. QUANTITY LIMITS

A. Etanercept (Enbrel) – Currently, etanercept (Enbrel) subcutaneous injection is limited to a 4-week supply in retail, a 6-week supply in the TMOP, and up to a 6-week supply at military treatment facilities (MTFs), based on instructions for use on the prescription. No multiple fills for multiple co-pays are allowed in TRRx and TMOP. The purpose of the quantity limit is to decrease potential wastage and excess cost if etanercept is prematurely discontinued.

The current recommended dose of etanercept for adult patients with rheumatoid arthritis (RA), psoriatic arthritis, or ankylosing spondylitis is 50 mg per week; for adult patients with psoriasis 50 mg twice weekly for 3 months, followed by 50 mg weekly as a maintenance dose; and for pediatric patients with juvenile rheumatoid arthritis 0.8 mg/kg weekly, up to a maximum of 50 mg per week. Etanercept was initially approved as a 25 mg twice-weekly injection for the treatment of RA and was available only as a 25-mg vial in sealed packages containing 4 vials (2 weeks supply for RA or 1-2 weeks supply for psoriasis). It recently became available as a 50 mg/mL pre-filled syringe, which is now the preferred method of dosing. The pre-filled syringes are packaged in sealed packages containing 4 syringes, causing difficulty in dispensing a 6-week supply.

The Committee agreed that, given the cost of etanercept and the existence of similar quantity limits for other biologics for the treatment of RA and/or psoriasis, a quantity limit should be retained, but adjusted to an 8-week supply in mail order and MTFs to allow for dispensing of whole packages.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 2 abstained, 1 absent) to recommend changing the quantity limits for etanercept (Enbrel) subcutaneous injection to a 4-week supply in retail, an 8-week supply in the TMOP program, and up to an 8-week supply at MTFs, based on instructions for use on the prescription.

B. Zolmitriptan (Zomig) – The current quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) is 8 tablets per 30 days, or 24 tablets per 90 days. Based on safety recommendations in triptan labeling, the safety of treating more than 4 migraine attacks in a 30-day period has not been established. Doses of both the tablets and nasal spray can be repeated after two hours if the first dose is ineffective.

Currently, zolmitriptan tablets are available in blister packs of 3 or 6 tablets. Zolmitriptan is also available as a nasal spray, packaged in boxes of 6 unit-dose nasal spray units. The current quantity limit for zolmitriptan nasal spray is 12 unit-doses per 30 days or 36 unit-doses per 90 days.

The Committee agreed that the quantity unit for zolmitriptan tablets should be increased to be consistent with the quantity limit for the nasal spray and to allow for dispensing of whole packages of zolmitriptan tablets.

COMMITTEE ACTION: The Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend changing the quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) to 12 tablets per 30 days, or 36 tablets per 90 days.

9. ALZHEIMER'S DRUG CLASS REVIEW. ACETYLCHOLINESTERASE INHIBITORS AND N-METHYL D-ASPARTATE (NMDA) RECEPTOR ANTAGONISTS

A. Alzheimer's Medications Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved acetycholinesterase inhibitors and NMDA receptor antagonists available in the U.S. for the treatment of Alzheimer's disease. The Alzheimer's disease therapeutic class was defined as the acetyl-cholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne) and tacrine (Cognex); and the NMDA receptor antagonist memantine (Namenda). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve month period ending July 31, 2005, 69,940 MHS patients were prescribed an acetylcholinesterase inhibitor or NMDA receptor antagonist. This class is now ranked 29th in MHS drug class expenditures at a cost of $65 million annually.

*1.) Efficacy. A*ll acetylcholinesterase inhibitors have FDA-approved indications for the treatment of mild to moderate Alzheimer's disease. The NMDA receptor antagonist

memantine is FDA approved for moderate to severe Alzheimer's disease. As there are no well-designed head-to-head trials comparing the four acetylcholinesterase inhibitors or memantine, the available placebo controlled trials and meta-analyses were reviewed.

Endpoints: Outcome measures used to assess the beneficial effects of the medications used in the treatment of Alzheimer's disease measure functioning in four categories which include cognitive function, global assessment, activities of daily living and behavioral disturbance. The two most consistent outcome measures used in randomized, controlled trials evaluate cognitive function (Alzheimer's Disease Assessment Scale, ADAS-Cog) and global assessment (Clinician's Interview Based Assessment of Change-Plus, CIBIC-Plus). The ADAS is an 11-item scale with scores ranging from 0 (no impairment) to 70 (very severe impairment). On average, untreated patients with moderate AD decline 7 to 11 points per year while treated patients with mild or severe disease decline 0 to 5 points per year. Generally, an improvement of 4 or more points is considered to be clinically meaningful, roughly equivalent to a six-month delay in cognitive decline. In clinical trials, improvement is characterized by a slowing of deterioration as opposed to improvement above baseline.

Mild to moderate Alzheimer's disease: The acetylcholinesterase inhibitors have been studied in mild to moderate Alzheimer's disease. Outcome measures included the ADAS-Cog and the CIBIC-plus. In well-designed, randomized, controlled trials involving donepezil vs. placebo, rivastigmine vs. placebo, galantamine vs. placebo, and tacrine vs. placebo, all of the achetylcholinesterase inhibitors showed statistically significant differences in the primary outcome measures compared to placebo. Systematic reviews by Cochrane, the British National Institute for Clinical Excellence (NICE), the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), and others have found that treatment with these drugs conferred a small clinical benefit when compared to placebo.

Moderate to severe Alzheimer's disease: Memantine is FDA-approved for treatment of moderate to severe Alzheimer's disease. Clinical trials comparing memantine to placebo used the ADAS-Cog and the Severe Impairment Battery (SIB) for primary outcome measures. In all of the trials, memantine showed a statistically and clinically significant improvement over placebo in the primary outcome measures.

Efficacy conclusion: All of the drugs used for Alzheimer's disease show statistically significant changes in cognition rating scores compared to baseline. Whether these results are clinically significant is debatable. There are no direct comparative trials available, but there is no evidence to suggest that any one Alzheimer's disease drug is more efficacious than another, when used according to FDA indications.

2.) Safety/Tolerability:

Serious effects – hepatotoxicity: Tacrine has been shown to cause elevated liver function tests (LFTs) in over 50% of patients, with 7% of patients experiencing LFT elevations greater than 10 times the upper limits of normal. In a major clinical trial, these LFT elevations led to an overall 72% discontinuation rate at the higher dosage range. The FDA requires a black box warning for the possibility of severe liver failure and death, and frequent monitoring of LFTs is mandated for patients using tacrine.

Side effects: Rivastigmine and galantamine are associated with a higher incidence of gastrointestinal (GI) side-effects and consequently require more complex titration than the other cholinesterase inhibitors or memantine. A complex titration schedule possibly affects

the likelihood that patients will adhere to these regimens. In clinical trials of memantine, the rate of patients discontinuing due to side effects was not statistically different from placebo.

Drug interactions: Donepezil and galantamine are metabolized by the CYP 450 enzyme system and thus may be prone to more drug interactions than other agents. However, it should be noted that interactions that increase levels of the Alzheimer's drugs are not generally considered to be clinically significant.

Safety/tolerability conclusion: The P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause hepatic injury. While minor differences exist among the other acetylcholinesterase inhibitors and memantine, none were considered significantly different with respect to major contraindications, drug interactions, and adverse drug reactions.

3.) Other Factors:

Titration and dosing frequency: A difference in ease of dosing and dose titration schedules exists among these agents. Donepezil and galantamine extended release are dosed once daily, the other agents are dosed twice daily (galantamine immediate release, rivastigmine and memantine) or four times daily (tacrine). There are no well-designed randomized controlled trials that demonstrate improved outcomes with once daily dosing of these agents, however once daily products have the theoretical advantage of yielding a lower burden on caregivers.

DoD Provider Preferences: In a PEC survey of DoD providers (neurologists, geriatricians, internists, and family practitioners), the majority of respondents favored products with once daily dosing. Most respondents stated that they avoided tacrine because of hepatotoxicity; all expressed a preference for donepezil based on ease of titration and familiarity; most said that they add or switch to memantine when acetylcholinesterase inhibitors failed to provide expected benefit; and most felt that these medications should not be discontinued once they stopped arresting cognitive decline, since patients decline precipitously once these medications were stopped.

Other Factors Conclusion: There is no evidence to suggest clinical superiority of any one Alzheimer's agent based on differences in dosing and titration schedules or DoD provider opinion.

Overall Clinical Effectiveness Conclusion: The P&T Committee concluded that tacrine has less clinical utility than the other acetylcholinesterase inhibitors used in the treatment of the cognitive symptoms of Alzheimer's disease. Furthermore the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the UF. The P&T Committee further concluded that safety considerations for tacrine would support a PA; however, due to the extremely low number of unique utilizers (single digits) any potential problem was felt to be self-limiting. The P&T Committee concluded that all the remaining acetylcholinesterase inhibitors have similar relative clinical effectiveness for treating mild to moderate dementia associated with Alzheimer's disease. The P&T Committee agreed that memantine has a place in therapy for the treatment of moderate to severe dementia associated with Alzheimer's disease. With regard to safety and tolerability, memantine has an adverse event rate similar to placebo.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that for the purposes of the UF clinical review, that tacrine possessed a safety disadvantage

relative to other available acetylcholinesterase inhibitors, but that all were similar in terms of effectiveness and clinical outcome, and that memantine has a place in therapy due to its indication for treatment of dementia in moderate to severe Alzheimer's disease.

B. Alzheimer's Drug UF Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in the Code of Federal Regulations (32 C.F.R. 199.21(e)(2)).

The first step in determining the relative cost effectiveness of the selected agents in this class was to conduct a cost-analysis to calculate the total weighted average cost per day of treatment for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review concluded, with the exception of tacrine, that all of the agents within the Alzheimer's drug class had similar relative clinical effectiveness (efficacy, safety and tolerability), a cost-minimization analysis (CMA) was selected. To adjust for the safety issues associated with the use of tacrine, the cost of monitoring liver function tests was added to the drug cost of tacrine in the CMA.

The cost analysis only considered drug costs. The results showed tacrine to be the acetylcholinesterase inhibitor with the lowest total weighted average cost per day of treatment across all points of service (MTF, TRRx, TMOP). The CMA, which considered lab costs for monitoring tacrine, showed that donepezil was the most cost-effective agent when the additional requirement of multiple liver function tests was taken into account.

The results of the above analyses were then incorporated into a budget impact analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of Alzheimer's drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the BIA further confirmed the results of the CMA. Donepezil was found to be the most cost-effective Alzheimer's drug overall.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative cost effectiveness analysis (CEA) of the Alzheimer's drugs presented. The P&T Committee concluded that the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the UF. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Alzheimer's drugs, the P&T Committee recommended that the status of tacrine be changed from formulary to non-formulary on the UF, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the UF with the formulary cost share. To address the safety concerns of tacrine, a PA for tacrine was initially considered. However, due to the extremely low number of unique utilizers (single digits) currently being treated with tacrine across the MHS, the P&T Committee felt the medical community was adequately aware of the risks associated with tacrine use, and safety concerns were already being appropriately addressed.

COMMITTEE ACTION. The P&T Committee, based upon its collective professional judgment, voted (10 for, 6 against, 2 abstained, 1 absent) to recommend non-formulary status for tacrine, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the UF at the formulary cost share.

C. Alzheimer's Drug UF Medical Necessity Criteria: Based on the clinical evaluation of tacrine, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for these agents.

1) Use of the formulary cholinesterase inhibitors (donepezil, galantamine, rivastigmine) is contraindicated, and the use of tacrine is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), and the patient is reasonably expected to tolerate tacrine.

3) Use of the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) resulted in therapeutic failure, and the patient is reasonably expected to respond to tacrine (therapeutic failure as outlined on medical necessity form).

4) The patient has previously responded to tacrine, and changing to the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) would incur unacceptable risk.

5) There is no alternative formulary agent.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to approve the medical necessity criteria.

D. Alzheimer's Drug UF Implementation Plan: Because of the low number of beneficiaries that would be affected by this formulary action (five patients known to be taking tacrine across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tacrine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary and/or provider must establish medical necessity for these agents. MTFs may (but are not required to) fill a prescription for tacrine written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION. The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Alzheimer's Drug Extended Core Formulary (ECF) Review and Recommendations. **T**he P&T Committee had previously determined that only one acetylcholinesterase inhibitor would be added to the ECF based on the clinical and cost effectiveness reviews. Additionally, the P&T Committee previously stated that one NMDA inhibitor (memantine) would be considered for addition to the ECF based on a favorable cost effectiveness evaluation. As a result of the economic evaluations presented, the P&T Committee recommended that donepezil be added to the ECF.

Conclusion: Donepezil was recommended for inclusion on the ECF.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to add donepezil to the ECF.

10. NASAL CORTICOSTEROIDS DRUG CLASS REVIEW

A. Nasal corticosteroid Relative Clinical Effectiveness Review: The Committee evaluated the relative clinical effectiveness of the six nasal corticosteroids marketed in the U.S.: beclomethasone dipropionate (Beconase AQ, Vancenase AQ and Vancenase AQ DS), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone propionate (Flonase), mometasone furoate (Nasonex), and triamcinolone acetonide (Nasacort AQ). Information regarding the safety, effectiveness, and clinical outcome of these drugs was considered. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) *Efficacy*: All of the nasal corticosteroids are FDA-approved for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Endpoints used in clinical trials included patient scoring on the total nasal symptom score (nasal blockage, rhinorrhea, sneezing and nasal itching) or total symptom score (itchy/burning eyes, tearing, redness). Two clinical reviews of seventeen randomized controlled trials evaluating various nasal corticosteroids determined equal efficacy amongst the nasal corticosteroids. Twenty placebo-controlled/head-to-head trials also concluded that nasal corticosteroids were equally effective at equipotent doses at relieving allergic rhinitis symptoms. Possible differences may lie in individual physician/patient preferences and population specific safety concerns.

   Efficacy Conclusion: Multiple clinical reviews over the past two decades suggest comparable efficacy between the nasal corticosteroids at relieving allergic rhinitis symptoms when used in equipotent doses.

2) *Safety and Tolerability*:

   a. Local effects:

      Transient local reactions, such as nasal irritation and stinging, sneezing, dryness, headaches, and occasional sore throat, are the common side effects seen with nasal corticosteroids. All of the aqueous nasal corticosteroid sprays can cause epistaxis, but in clinical trials, the placebo spray also had an appreciable rate of epistaxis. Other, rarely reported local adverse events include nasal septum ulceration and septal perforation. There is no evidence to suggest that one nasal corticosteroid is more likely to cause local adverse effects than another. According to package insert data, approximately 2-3% of patients discontinue a nasal corticosteroid treatment due to adverse events.

   b. Systemic Adverse Events:

      i. *Hypothalmic adrenal axis (HPA) suppression:* HPA-axis suppression is a concern with all corticosteroids (oral, inhaled, and nasal) as it can progress to acute adrenal crisis in all ages. Two separate review articles, one evaluating 19 randomized clinical trials and the other 7 additional randomized clinical trials, found no significant differences between the nasal corticosteroids in suppression of the HPA-axis. The true clinical relevance of nasal corticosteroid use and any resultant significant adrenal gland suppression/adrenal crisis is difficult to ascertain as the trials report changes in surrogate markers (e.g., urinary cortisol excretion, serum

cortisol, or adrenocorticotropin hormone concentration) and are not consistent across testing methods. Placebo-controlled trials show similar HPA-axis suppression between placebo and nasal corticosteroids, as evidenced by reductions in lab values, while comparisons with oral prednisone showed greater suppression than nasal corticosteroids. It is unlikely that the risks of HPA-axis suppression differ among nasal corticosteroids, although theoretically fluticasone propionate and mometasone furoate may confer lower risk due to lower bioavailability than the others.

ii. *Growth retardation:* All inhaled and nasal corticosteroids are required by the FDA to have a warning label in their package inserts regarding the potential risk of growth suppression. Regular monitoring is especially necessary for children receiving multiple corticosteroid therapies, as excessive corticosteroid doses can lead to proven growth suppression. Head-to-head trials and placebo-controlled trials have shown conflicting results among the nasal corticosteroids in outcomes measuring lower leg growth velocity and standing height. Inconsistency across trials in growth measurement and study methodology make it difficult to interpret actual growth suppression and to determine the possible effects of nasal corticosteroids when predicting future pediatric growth velocity. In general, nasal corticosteroids should be used with care in children by titrating to the lowest effective dose so to keep growth suppression to a minimum.

iii. *Cataracts:* A large retrospective evaluation from the UK compared the use of nasal corticosteroids in over 280,000 patients with and without diagnosed cataracts. Over 70% of the patients were solely receiving beclomethasone dipropionate. No increased association was found between nasal steroid use and cataract formation; however, patients receiving chronic oral corticosteroid therapy were found to have an increased frequency of cataract formation. Excessive doses of nasal corticosteroids can lead to rare effects of cataracts. There is insufficient evidence to predict whether one nasal corticosteroid is more likely to cause cataracts than the other.

Overall safety conclusion: Nasal irritation, epistaxis, and rhinorrhea are the most common local adverse events, and are equally likely to occur with any of the nasal corticosteroids. For systemic effects (HPA-axis suppression, growth suppression, and cataract formation), there is no definitive evidence that one nasal corticosteroid is more likely to cause these effects than another. Depending on the severity of allergic rhinitis symptoms, the benefits of nasal corticosteroids may outweigh the risks of systemic adverse effects. According to the package inserts, the risk of systemic effects is increased when higher than normal amounts of nasal corticosteroids are used.

3) *Other Factors:*

a. *Dosing frequency*: Most of the nasal corticosteroid products are marketed for once daily administration. Budesonide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide are dosed once a day, while beclomethasone dipropionate and flunisolide require at least twice to three times daily dosing. Dosing may contribute to patient adherence or patient preference for an individual product. Theoretically, once daily dosing may result in improved patient compliance vs. products requiring multiple daily dosing.

b. *Kinetics/dynamics*: Molecular weight, lipophilicity, and thixotropy are types of pharmacokinetic measures used to differentiate potency between the nasal

corticosteroids. When evaluating potency, varying results have been reported between nasal corticosteroids, as experimental set-ups in the laboratory setting do not conclusively correlate with what providers may witness in their patients. There is no evidence that differences in these kinetic/dynamic parameters are linked to differences in clinical outcomes.

c. *Formulation*: The nasal aerosol formulations of Beconase (beclomethasone dipropionate), Vancenase (beclomethasone dipropionate), and Rhinocort (budesonide) have declined in popularity as physicians and patients have chosen the ease and convenience of use with the newer aqueous nasal formulations (Beconase AQ, Vancenase AQ, Vancenase AQ DS, Rhinocort AQ, Flonase, Nasonex, Nasacort AQ).

d. *Pediatric Populations:* All the nasal corticosteroids are indicated for use in children six years of age or older, but fluticasone propionate is indicated for children down to the age of four years, and mometasone furoate is indicated for use in children as young as two years old.

e. *Pregnancy:* The only nasal corticosteroid with a FDA Category B (low risk in humans) rating is budesonide. This indication was given primarily due to a retrospective epidemiological study reviewing data from three Swedish registries and a pregnancy outcome study (Steroid Treatment and Regular Therapy [START] study) of over 6,000 infants. All the other nasal corticosteroids are rated Category C (risk cannot be ruled out). There is one placebo-controlled human study that focused specifically on the safety and efficacy of maternal nasal corticosteroid (fluticasone propionate) use during pregnancy. There were no differences found between the treatment and placebo groups in pregnancy outcomes. Pregnant patients are still advised to discuss benefit versus risk ratios of nasal corticosteroid use with their OB/GYN provider.

f. *Patient preference/tolerability*: Patient's attitudes toward features such as taste, odor, irritation, and moistness may attribute to adherence of certain nasal corticosteroids. Patient preference may play a role in differentiating between the nasal corticosteroids, but the available clinical data are poor, and no one nasal corticosteroid has proven superior to the others in patient preference trials. More well-designed, head-to-head randomized, controlled trials are needed to support a conclusion that one nasal corticosteroid is superior to another in tolerability or compliance.

Conclusion for Other Factors: Minor differences exist among the agents in terms of frequency of dosing, kinetic/dynamic parameters, pediatric labeling, and use in pregnancy.

Overall Clinical Effectiveness Conclusion: The DoD P&T Committee concluded that: 1) in equipotent doses, the nasal corticosteroids are equally effective at relieving symptoms of allergic rhinitis; 2) in equipotent doses the nasal corticosteroids have similar local side effect profiles; 3) there is a lower risk of systemic adverse effects (HPA-axis suppression, growth retardation, cataract formation) when nasal corticosteroids are used according to labeled dosing instructions; however, there is no evidence that systemic effects are likely to occur more frequently with one agent versus another; 4) products that are dosed once daily may have advantages in terms of patient preference over products requiring multiple daily dosing; 5) minor differences in pharmacokinetic/dynamic factors (thixotropy, molecular weight, lipophilicity) have not translated into differences in clinical outcomes; 6) mometasone furoate is indicated for use in pediatric patients as young as two years of age; 7) budesonide is rated pregnancy category B, while fluticasone propionate has evidence from one trial that pregnancy

outcomes were not adversely affected with use during pregnancy; and 8) there is no clear difference between the nasal corticosteroids in terms of patient preference and tolerability.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that, for the purposes of the UF clinical review, none of the nasal corticosteroids have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other nasal corticosteroids.

B. Nasal Corticosteroids Relative Cost Effectiveness: The P&T Committee evaluated the relative cost effectiveness of the agents considering possible differences in safety, tolerability, and effectiveness in accordance with 32 CFR 199.21 (e)(2).

Two separate economic evaluations were performed, a pharmacoeconomic analysis and a BIA. From the proceeding relative clinical effectiveness evaluation, the P&T Committee determined that nasal corticosteroids have similar relative clinical efficacy, but some small differences in terms of dosing frequency, use in pregnancy, use in pediatric populations, and DoD provider preferences. The agents within the nasal corticosteroid therapeutic class were thus shown to differ slightly in relative clinical effectiveness.

The above stated differences in the nasal corticosteroids have not been evaluated in clinical trials for their effect on treatment outcomes. The PEC surveyed DoD medical providers to evaluate their opinion on these difference. The PEC conducted two cost analyses, one analysis with no effectiveness measure, and the second analysis incorporating the results of the survey as an effectiveness measure.

In the first cost analysis of the cost per day of therapy across DoD alone, the results showed that flunisolide was the most effective; budesonide, fluticasone propionate, mometasone furoate and triamcinolone acetonide (not in rank order) were less cost effective; and beclomethasone was not cost effective.

In the second cost analysis of the cost per day of therapy across DoD incorporating the effectiveness measure, the results showed that (all in alphabetical order) flunisolide, fluticasone propionate and mometasone furoate were the most cost effective, and beclomethasone dipropionate, budesonide and triamcinolone acetonide were not cost effective.

Both cost analyses were incorporated into a BIA, to analyze the cost to the DoD under various formulary status configurations, and to estimate the cost of formulary changes to the DoD. The results of the BIA revealed that the best combination of agents to meet DoD's clinical and cost effectiveness goals is the group of formulary agents that included flunisolide, fluticasone propionate, and mometasone furoate. These results matched the results from the cost analysis incorporating the effectiveness measure derived from the survey of DoD providers.

Conclusion: The P&T Committee, based on its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 3 absent) to accept the nasal corticosteroid CEA presented by the PEC. The P&T Committee concluded that flunisolide, fluticasone propionate, and mometasone furoate had similar cost effectiveness, and that they had greater cost effectiveness than beclomethasone dipropionate, budesonide, or triamcinolone acetonide.

Class Review Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness evaluations, and other relevant factors, the P&T Committee recommended that beclomethasone dipropionate, budesonide, and triamcinolone acetonide be classified as non-formulary under the UF, and that flunisolide, fluticasone propionate, and mometasone furoate be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based on its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend formulary status for flunisolide, fluticasone propionate, and mometasone furoate; and non-formulary status for beclomethasone dipropionate, budesonide, and triamcinolone acetonide under the UF.

C. Nasal Corticosteroids UF Medical Necessity Criteria: Based on the clinical evaluation of the nasal corticosteroids and the conditions for establishing medical necessity for non-formulary medications provided for in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of all formulary nasal corticosteroids (flunisolide, fluticasone propionate, mometasone furoate) is contraindicated, and the use of a nonformulary nasal corticosteroid (beclomethasone dipropionate, budesonide, triamcinolone acetonide) is not contraindicated.
2) The patient has experienced or is likely to experience significant local adverse events (epistaxis, pharyngitis, nasal irritation) from all formulary nasal corticosteroids, and the patient is reasonably expected to tolerate a non-formulary nasal corticosteroid.
3) Use of all the formulary nasal corticosteroids resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary nasal corticosteroid (therapeutic failure as outlined on the medical necessity form).

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to approve the medical necessity criteria.

D. Nasal corticosteroid UF Implementation Plan: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period.

COMMITTEE ACTION: The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

E. Nasal Corticosteroids Basic Core Formulary (BCF) Review and Recommendations. **T**he P&T Committee reviewed the nasal corticosteroids recommended for inclusion on the UF to select the BCF nasal corticosteroid(s). It had been previously decided that at least one, but no more than two, nasal corticosteroids would be added to the BCF, based on the outcome of a preliminary clinical effectiveness review and DoD needs assessment conducted at the August 2005 P&T Committee meeting.

A cost analysis was performed using prices submitted for BCF status. While flunisolide had a lower cost per day of therapy than fluticasone propionate and mometasone furoate, fluticasone propionate provided the best overall value to DoD, in terms of a competitive price, most preferred dosing frequency (once a day), and overwhelming preference by DoD providers in all but a small subpopulation of DoD patients. The Committee saw no compelling need to have a second agent on the BCF.

Conclusion: The P&T Committee recommended retaining fluticasone on the BCF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend fluticasone as the BCF agent.

11. ANTIDEPRESSANTS GROUP 1 (AD1) DRUG CLASS REVIEW

A. AD1 UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of antidepressant medications. The drug class reviewed included all U.S. marketed antidepressants, except monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which will be reviewed separately. Individual medications are outlined in the table below. Although the receptor-binding characteristics and pharmacological classification of these medications vary, the Committee agreed that there is sufficient overlap in their clinical use to review them as a single class of medications.

The Committee considered information concerning the safety, tolerability, efficacy, and clinical outcome of the AD1s. Like many medications, the AD1s have multiple potential uses in addition to the treatment of depression. The Committee's review focused most heavily on the use of these agents for depression, but also considered the clinical effectiveness of individual agents in the treatment of other psychiatric and non-psychiatric conditions. FDA-approved indications for the AD1s are outlined in the table below. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21.

Generic Name	**Brand Name**	**FDA-Approved Indications** (as of July 2005)
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram	Celexa, generics	MDD
Escitalopram	Lexapro	MDD, GAD
Fluoxetine	Prozac, generics	MDD, OCD, PD, bulimia (pediatric labeling MDD, OCD)
Fluoxetine 90 mg caps (weekly regimen)	Prozac Weekly	MDD (maintenance of response only)
Fluoxetine (special packaging)	Sarafem	PMDD
Fluvoxamine	Generics	OCD (pediatric labeling)*
Paroxetine HCl	Paxil, generics	MDD, GAD, OCD, PD, PTSD, SAD
Paroxetine HCl controlled release	Paxil CR	MDD, PD, PMDD, SAD
Paroxetine mesylate	Pexeva	MDD, OCD, PD
Sertraline	Zoloft	MDD, OCD, PD, PTSD, PMDD, SAD (pediatric labeling OCD)
Serotonin – Norepinephrine Reuptake Inhibitors (SNRIs)		
Duloxetine	Cymbalta	MDD, DPNP
Venlafaxine	Effexor, generics	MDD
Venlafaxine extended release	Effexor XR	MDD, GAD, SAD
Serotonin-2 Antagonist/Reuptake Inhibitors (SARIs)		
Nefazodone	Generics	MDD
Trazodone	Desyrel, generics	MDD
Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)		
Bupropion	Wellbutrin, generics	MDD
Bupropion sustained release	Wellbutrin SR, generics	MDD
Bupropion extended release	Wellbutrin XL	MDD
Alpha-2 Receptor Antagonists		
Mirtazapine	Remeron, generics	MDD

MDD = Major Depressive Disorder, GAD = Generalized Anxiety Disorder, OCD = Obsessive Compulsive Disorder, PD = Panic Disorder, PTSD = Posttraumatic Stress Disorder, PMDD = Premenstrual Dysphoric Disorder; SAD = Social Anxiety Disorder; DPNP = Diabetic Peripheral Neuropathic Pain

*Fluvoxamine is approved for depression in other countries, including Canada.

1) *Safety and Tolerability:* The Committee assessed the comparative safety and tolerability of the AD1s, including common adverse effects, rare but serious adverse effects, potential for drug interactions, safety of use in special populations, the risk of adverse effects when discontinuing use (discontinuation syndrome), and safety/tolerability issues with special formulations of paroxetine, fluoxetine, and bupropion.

   a. Common Adverse Effects

      i. Adverse effect profiles of the AD1s are known to differ. A particular agent made be chosen to either avoid a known side effect, or to take advantage of a known side effect clinically (e.g., selecting an antidepressant likely to cause sedation for an elderly patient who is having difficulty sleeping).

      ii. Differences in clinical trials designs, patient populations, and methods of collecting adverse effect information make direct comparison of adverse effects difficult. Head-to-head trials comparing two or more AD1s are typically not powered to find significant differences in discontinuation rates due to adverse effects. Discontinuation rates in clinical trials are typically lower than in actual practice. In addition, many adverse effects tend to resolve with continued treatment and may or may not affect adherence to therapy or clinical outcomes. There are few long-term, prospective head-to-head trials under "real-world" conditions.

      iii. Overall, bupropion, fluoxetine, and paroxetine appear to be most associated with agitation/activation, while nefazodone, trazodone, and mirtazapine appear most likely to cause sedation. Anticholinergic effects have been reported with paroxetine and fluvoxamine. Gastrointestinal symptoms (e.g., nausea) are commonly reported with SSRIs, may be more common with venlafaxine, and may be less common with nefazodone, trazodone, bupropion, or mirtazapine. Diarrhea may occur more commonly with sertraline, compared to bupropion sustained release (SR), paroxetine, and mirtazapine.

      iv. Sexual dysfunction appears less likely to occur with bupropion, mirtazapine, trazodone, or nefazodone than with the SSRIs or SNRIs. There have been multiple trials supporting a lower risk of sexual dysfunction with bupropion compared to SSRIs.

      v. Elevations in blood pressure have been reported with the SNRIs (venlafaxine and duloxetine). This may be more frequent with venlafaxine than with duloxetine, although comparative data are lacking. There have also been reports of increases in blood pressure with bupropion and fluoxetine. Clinically relevant and statistically significant increases in cholesterol have been reported in a small percentage of patients treated with venlafaxine.

      vi. Most serotonergic antidepressants are associated with adverse effects when abruptly discontinued. This discontinuation syndrome appears to be related to elimination half-life, with symptoms occurring more frequently with medications with shorter half-lives (Propensity for syndrome among SSRIs)). fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine (half-life 6 days). Venlafaxine, which has a short half-life, may be associated with more discontinuation symptoms than the SSRIs. Comparative information with duloxetine is unavailable, but discontinuation symptoms have been reported. Little information is available concerning discontinuation symptoms with trazodone; there have been only anecdotal

reports with nefazodone and mirtazapine. Discontinuation symptoms from abrupt discontinuation of bupropion, which has little effect on the serotonergic system, appear uncommon.

b. Rare but Serious Adverse Effects/Use in Special Populations

i. Abnormal bleeding, movement disorders, and hyponatremia have been reported rarely with SSRIs; there are insufficient data to determine if any one SSRI is associated with a higher risk.

ii. The manufacturer of duloxetine issued a "Dear Doctor" letter in Oct 2005 expanding existing recommendations to avoid use of duloxetine in patients with substantial alcohol use to include patients with pre-existing liver disease, following reports of hepatic injury in patients receiving duloxetine. Duloxetine is not recommended in patients with any degree of hepatic insufficiency due to substantially reduced clearance. Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma because it can cause mydriasis, and should be used in caution in patients receiving medications or having medical conditions that slow gastric emptying.

iii. Bupropion is contraindicated in patients with seizure disorder or conditions predisposing to seizure disorder or at increased seizure risk due to abrupt discontinuation of alcohol or sedatives. The risk of seizure in patients without predisposing factors appears low (0.1-0.4% at doses of 300-450 mg/d), but increases sharply at higher doses. Bupropion should be used with caution in hepatic impairment and extreme caution in severe hepatic cirrhosis.

iv. Nefazodone has a black box warning stating that it should not be used in patients with active liver disease or pre-existing transaminase elevation.

v. Trazodone should be used with caution in patients with cardiac disease. Priapism has been rarely reported with trazodone.

vi. Agranulocytosis has been rarely reported with mirtazapine.

vii. All AD1s are Pregnancy Category C except bupropion, which is Pregnancy Category B. Non-teratogenic adverse effects (e.g., respiratory distress) have been reported with serotonergic antidepressants when given in the third trimester. A recent epidemiological study cited in new labeling for paroxetine reported a greater than two fold increase in risk for birth defects in the first trimester with paroxetine compared to other SSRIs.

viii. A recent FDA analysis showed a higher risk of suicidal ideation or suicidality during the first few months of treatment with antidepressants in children and adolescents (4% vs. 2% with placebo). The FDA has issued a Public Health Advisory urging particular caution in watching for signs of worsening depression or suicidal thoughts at the beginning of antidepressant therapy or whenever the dose is changed, and this information has been added to antidepressant labeling in general. Despite a number of meta-analyses and observational studies addressing the risk of suicidality with antidepressants, no one antidepressant appears to be consistently associated with a higher risk of suicidality. The FDA continues to analyze data; adult results are expected in 2006.

c. Potential for drug interactions

i. Unlike fluoxetine, paroxetine, and fluvoxamine, which are metabolized by the cytochrome P450 system [fluoxetine and paroxetine inhibit P450 2D6 and fluvoxamine inhibits multiple P450 isoenzymes], sertraline, citalopram, and escitalopram are considered the least likely to result in significant drug interactions.

ii. Of the SNRIs, venlafaxine is primarily eliminated renally and has minimal effect on P450 isoenzymes; clinically meaningful drug interactions appear unlikely. Duloxetine has a moderate inhibitory effect on P450 2D6, is metabolized by 2D6 and 1A2, and may have increased hepatotoxicity in patients with substantial alcohol use. In addition it has a potential interaction with drugs affecting gastric acidity.

iii. Nefazodone, which inhibits 3A4, may interact with multiple medications. Information with trazodone is unclear. Bupropion does not appear to have substantial drug interactions, although it should not be used with drugs that lower the seizure threshold. Mirtazapine appears unlikely to cause substantial drug interactions, since it is metabolized by multiple pathways and does not appear to be a potent inhibitor of 2D6, 1A2, or 3A4.

d. Special Formulations

i. *Paroxetine controlled release (CR)* - The CR formulation of paroxetine (Paxil CR) is designed to release its contents over 4-5 hours after the medication reaches the small intestine; the intent is to reduce the incidence of nausea and related GI symptoms compared to the immediate release (IR) product. Both products are given once daily.

Based on pooled data from two 12-week, double-blind, randomized, placebo-controlled MDD trials comparing paroxetine CR and IR at similar doses [Golden et al. *J Clin Psychiatry* 2002; 63:577-84], patients receiving paroxetine CR showed significantly lower rates of nausea in the first week compared to paroxetine IR (14% vs. 23%, $p \leq 0.05$). Nausea rates began to decline in both groups starting in week 2, with no significant differences after week 1, and no numerical advantage for the CR formulation after week 3. Discontinuations due to adverse effects occurred in 6% of patients in the placebo group, 10% of patients in the paroxetine CR group ($p=0.14$ vs. placebo), and 16% of patients in the paroxetine IR group ($p=0.0008$ vs. placebo). There was no statistically significant difference between the CR and IR group. Discontinuations due specifically to nausea occurred in 3% of patients in the CR group, 4% in the IR group, and 0.5% in the placebo group.

There are no head-to-head trials comparing paroxetine CR to other SSRIs, and thus no direct evidence comparing rates of nausea or discontinuation due to adverse effects.

ii. *Fluoxetine 90-mg delayed release capsules (Prozac Weekly)* – Fluoxetine has a much longer half-life than other SSRIs, a fact that is exploited by the 90-mg weekly formulation. Fluoxetine weekly has an enteric coating that delays the onset of absorption by 1 to 2 hours relative to IR formulations, but does not otherwise extend the release of fluoxetine. It is FDA-approved only for maintenance of response in patients with MDD, not for initial therapy. The advantage of fluoxetine weekly is patient convenience and potentially increased adherence to treatment. This point has not been well-established, although one study reported greater compliance with the once-weekly regimen compared to 20 mg daily during a 3-month continuation phase [Claxton et al. *J Clin Psychiatry* 2000; 61:928-32]. Since compliance during a clinical

trial may be very different from compliance in practice, it is unclear whether this represents a real advantage for fluoxetine weekly. It is not clear whether fluoxetine 90 mg weekly is equivalent to fluoxetine 20 mg/d in maintaining response.

iii. *Fluoxetine in special packaging for premenstrual dysphoric disorder (PMDD) (Sarafem)* – Fluoxetine 10 and 20 mg capsules are available in special packaging and with special labeling for the treatment of PMDD, under the name of Sarafem. Usual dosing is 20 mg/day; the product does not appear to differ from the other branded fluoxetine product (Prozac), except for differences in the color of the capsules. When Sarafem was first introduced, the manufacturer stated the intent was to allow patients with PMDD to avoid the stigma associated with use of antidepressants.

iv. *Bupropion extended release (Wellbutrin XL)* – The main advantage offered by the extended release bupropion product (Wellbutrin XL) compared to sustained release bupropion is once-daily vs. twice-daily administration. This is not regarded as an overwhelming advantage for medications in most disease states, although there is some evidence that patients have poorer adherence to twice daily versus once daily regimens and that patients with depression have worse adherence to medication than non-depressed patients. In the case of bupropion sustained release, package labeling advises separating doses by 8 hours. Since patients are usually advised not to take bupropion late in the day due to its activating properties, bupropion sustained release is likely to be dosed in the morning and early afternoon, which may present more logistical problems than typical twice-daily regimens. Bupropion extended release may be taken as a single dose in the morning.

Safety /Tolerability Conclusion: The Committee concluded that adverse effect profiles differ across AD1s, but there are little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. The Committee agreed that fluvoxamine, fluoxetine, paroxetine, and duloxetine have a generally higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine. Available evidence addressing the likelihood of discontinuation syndrome with SSRIs tends to correlate with a rank-order of risk based on half-life (greatest to least risk). fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine. Venlafaxine has a short half-life, and may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar based on half-life. Discontinuation symptoms appear uncommon with bupropion; data are limited with trazodone, nefazodone, and mirtazapine. Rare but serious adverse effects appear to be associated with duloxetine (recent case reports of hepatotoxicity), bupropion (seizure), nefazodone (hepatotoxicity), mirtazapine (agranulocytosis), and trazodone (priapism). Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk).

2) Efficacy/Clinical Outcomes

a. Major Depressive Disorder (MDD)

i. *SSRIs vs. SSRIs* – Of 23 head-to-head trials comparing SSRIs to other SSRIs, very few reported any significant differences between SSRIs. These trials were mostly of short

duration, with many lasting only 6-8 weeks. They typically assessed changes on the two most commonly used depression scales, the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). Most of these trials reported response rates (≥ 50% decrease on the HAM-D or MADRS), with a few reporting remission rates (percent of patients achieving a certain HAM-D or MADRS score). A 9-month "real-world" effectiveness trial comparing paroxetine, sertraline, and fluoxetine in primary care patients with depression as determined by the primary care provider [Kroenke et al. *JAMA* 2001; 286:2947-55] found no significant differences in efficacy among these three SSRIs. Two meta-analyses of response rates performed by Oregon reviewers showed no differences between paroxetine and fluoxetine, and a very slight and probably clinically insignificant difference (RR 1.10, 95% CI 1.01-1.22) favoring sertraline over fluoxetine. Only two trials reported statistically significant differences in efficacy [Lepola et al. *Int Clin Psychopharmacol* 2003; 18(4):211-7; Moore et al. *Int Clin Psychopharmacol* 2005; 20(3):131-7]. Both of these trials reported greater efficacy with escitalopram compared to citalopram. A third trial comparing citalopram and escitalopram showed no significant differences [Burke et al. *J Clin Psychiatry* 2002; 53:331-6]. Results of an unpublished trial comparing escitalopram to sertraline supplied by the manufacturer of escitalopram showed no significant differences between these two SSRIs. There is no published data supporting greater efficacy for paroxetine CR or fluoxetine weekly, compared to the original formulations or to other SSRIs.

ii. *Venlafaxine vs. SSRIs* – There are a number of head-to-head trials and meta-analyses comparing venlafaxine and various SSRIs, including paroxetine, fluoxetine, sertraline, and escitalopram. Overall, few of these trials reported significant differences between SSRIs and venlafaxine. Two meta-analyses comparing venlafaxine to fluoxetine showed a modest efficacy advantage for venlafaxine [Smith et al. *Br J Psychiatry* 2002; 180:364-404; Oregon reviewers], although venlafaxine was associated with more adverse effects. Two 8-week, randomized, controlled trials comparing venlafaxine extended release (venlafaxine XR) to escitalopram showed no differences in efficacy [Montgomery et al. *Neuropsychobiol* 2004; 50(1):57-64; Bielski et al. *J Clin Psychiatry* 2004; 65(9):1190-6].

iii. *Duloxetine vs. SSRIs* – There are no published head-to-head trials designed to compare duloxetine with other AD1s, although limited comparative data are available from six 8-week duloxetine trials that included active control arms (fluoxetine or paroxetine). However, these trials were not powered to directly compare active treatments; fluoxetine or paroxetine doses were limited to 20 mg/d while duloxetine was dosed from 40 to 120 mg/d. Duloxetine 60 mg/d appeared generally comparable to escitalopram 10 mg/d based on results of an unpublished, randomized, placebo-controlled trial supplied by the manufacturer of duloxetine.

Based on *in vitro* data, duloxetine appears to bind more equally to serotonin and norepinephrine reuptake transporters than venlafaxine. This "more balanced" inhibition is theorized to have favorable effects on pain, since inhibitory modulation of pain signals in neural pathways occurs via release of both serotonin and norepinephrine. A complementary argument is that duloxetine may be a better treatment than other antidepressants for depressed patients presenting with "painful symptoms of depression." Support for this argument is limited. Patients with depression commonly present with physical (somatic) symptoms, including pain,

which resolve along with mood symptoms following anti-depressant treatment. Brannan et al. [*J Psychiatric Res* 2005; 39:43-53] reported results of a randomized, placebo-controlled trial assessing the effects of duloxetine on pain in depressed patients with painful symptoms at baseline. The mean difference in Brief Pain Index (BPI) average pain scores (0=no pain; 10 = as bad as you can imagine) was consistently a little less than a point lower with duloxetine vs. placebo, starting at week 1. The difference reached statistical significance at weeks 1, 2, and 5, but was not significantly different at endpoint (p=0.066). Whether these results translate into a real advantage for duloxetine compared to other antidepressants in depressed patients presenting with somatic symptoms of pain is unclear.

iv. *Venlafaxine vs. duloxetine* – There are no published head-to-head trials comparing venlafaxine and duloxetine for the treatment of depression. A 2005 meta-analysis [Vis et al. *Ann Pharmacother* 2005; 39:1789-807] comparing placebo-controlled trials with venlafaxine and duloxetine did not show a statistically significant difference between duloxetine and venlafaxine XR, although remission and response rates tended to favor venlafaxine XR. A summary of pooled results of two unpublished, double-blind, MDD randomized, controlled trials comparing duloxetine and venlafaxine supplied by the manufacturer of duloxetine showed no significant differences between venlafaxine and duloxetine based on Global Benefit-Risk assessment (a statistical method that weighs both efficacy and adverse effects), remission rate, or change from baseline in HAM-D total score.

v. *Bupropion* – Based on six head-to-head trials and one meta-analysis, bupropion appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline). There are no published data supporting greater efficacy for bupropion extended release, compared to the immediate or sustained release formulations of bupropion or to other SSRIs.

vi. *Mirtazapine* – Based on five head-to-head trials, mirtazapine appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline).

vii. *Nefazodone* – Based on three head-to-head trials, nefazodone appeared similar in efficacy to SSRIs (fluoxetine, paroxetine, and sertraline). One of these studies included pooled data from three trials with identical protocols focusing primarily on effects of nefazodone or fluoxetine on sleep quality; nefazodone appeared to significantly improve sleep quality compared to fluoxetine.

viii. *Trazodone* – Based on five 6-week trials, trazodone appeared similar in efficacy to fluoxetine and bupropion, and possibly less efficacious than venlafaxine, although insufficient evidence exists to draw any real conclusion. At present, the major role of trazodone in depressed patients appears to be as an adjunctive medication for the treatment of insomnia.

ix. *Treatment of depression in children and adolescents* – Fluoxetine is the only antidepressant FDA-approved for MDD in children and is used in most pediatric MDD trials. The FDA has concluded that only fluoxetine has been shown to have a favorable risk-benefit profile in pediatric patients, based on the fact that it is the only antidepressant that has demonstrated efficacy in a pediatric population.

b. *Other Psychiatric Conditions*:

i. *Generalized Anxiety Disorder (GAD)*. Venlafaxine, paroxetine, and escitalopram are FDA-approved for treatment of GAD. Sertraline appears to be efficacious for the

treatment of GAD based on results of a large published, placebo-controlled trial [Allgulander et al. *Am J Psychiatry* 2004; 161:1642-9]. Two head-to-head trials, one comparing paroxetine and sertraline and the other comparing paroxetine and escitalopram, reported no difference between active treatments based on reductions in anxiety (HAM-A) scores [Ball et al. *J Clin Psychiatry* 2005; 66:94-9; Bielski et al. *Ann Clin Psychiatry* 2005; 17:65-9].

ii. *Obsessive Compulsive Disorder (OCD).* Fluoxetine, fluvoxamine, paroxetine, and sertraline are FDA-approved for the treatment of OCD; fluoxetine, sertraline, and fluvoxamine are approved for use in children and adolescents. At least four separately conducted meta-analyses, one focusing on trials in pediatric patients, showed no significant difference between included SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline). Two head-to-head trials, one comparing sertraline and fluoxetine, and the other comparing paroxetine and venlafaxine XR, showed no difference in efficacy between active treatments [Bergeron et al. *J Clin Psychopharmacol* 2002; 22(2):148-54; Denys et al. *J Clin Psychopharmacol* 2003; 23(6):568-75]. Citalopram appears to be effective for the treatment of OCD based on results of a long-term (> 6 month) trial [Montgomery et al. *Int Clin Psychopharmacol* 2001; 16:75-86].

iii. *Panic Disorder (PD).* Fluoxetine, paroxetine, and sertraline are FDA-approved for panic disorder. A head-to-head trial comparing sertraline and paroxetine showed no significant differences in efficacy [Bandelow et al. *J Clin Psychiatry* 2004; 65:405-13]. Fluvoxamine and venlafaxine XR appear efficacious based on short-term, placebo-controlled trials. Citalopram appears to be efficacious for panic disorder based on results of a placebo-controlled trial with a 1-year extension [Wade et al. *Br J Psychiatry* 1997; 170:549-53; Lepola et al. *J Clin Psychiatry* 1998; 59:528-34]. A 10-week trial comparing both citalopram and escitalopram to placebo reported significant improvement with both active treatments on many measures, including quality of life, although only escitalopram significantly reduced the frequency of panic attacks compared to placebo [Stahl et al. *J Clin Psychiatry* 2003; 64:1322-7]. This trial was not designed to compare active medications

iv. *Premenstrual Dysphoric Disorder (PMDD).* Fluoxetine (as Sarafem), paroxetine, and sertraline are FDA-approved for the treatment of PMDD. Evidence supporting efficacy is also available for citalopram, fluvoxamine, and venlafaxine [Wyatt et al. *Cochrane Database Syst Rev* 2002; 4:CD001396; Freeman et al. *Obstet Gynecol* 2001; 98(5 Pt 1):737-44]. There are no head-to-head trials.

v. *Post-Traumatic Stress Disorder (PTSD).* Sertraline and paroxetine are FDA-approved for PTSD. Mirtazapine may be efficacious in PTSD based on a 6-week, head-to-head, open-label trial with sertraline which showed a higher percentage of responders with mirtazapine [Chung et al. *Human Psychopharmacol* 2004; 19:489-94]. Published data supporting efficacy of fluoxetine for PTSD include two small, placebo-controlled trials, one of which showed a significant effect on prevention of relapse over a 6-month period [Connor et al. *Br J Psychiatry* 1999; 175:17-22; Davidson et al. *J Clin Psychopharmacol* 2005; 25:166-9].

vi. *Social Anxiety Disorder (SAD).* Paroxetine, sertraline, and venlafaxine are FDA-approved for the treatment of SAD. Two placebo-controlled trials comparing venlafaxine XR and paroxetine showed no differences in efficacy between active treatments, although venlafaxine XR appeared to be associated with a faster onset of

action in one trial [Liebowitz et al. *Arch Gen Psychiatry* 2005; 62:190-8; Allgulander et al. *Human Psychopharmacol* 2004; 19:387-96]. Escitalopram appears efficacious for SAD based on results of a placebo- and paroxetine-controlled trial [Lader et al. *Depress Anxiety* 2004; 19:234-40], and an additional 12-week, placebo-controlled trial [Kaspar et al. *Br J Psychiatry* 2005; 186:222-6]. A small trial with fluvoxamine showed significant improvement in efficacy compared to placebo [Stein et al. *Am J Psychiatry* 1999; 156:756-60].

vii. *Bulimia*. Fluoxetine is the only AD1 that is FDA-approved for treatment of bulimia. The majority of data (and all the larger trials) supporting efficacy of SSRIs for bulimia/binge eating disorder were done with fluoxetine. Although there are small trials with other AD1s, data are insufficient to draw conclusions about the efficacy of other AD1s for bulimia.

c. *Non-psychiatric conditions*

i. Diabetic peripheral neuropathic pain (DPNP)

A recent Cochrane systematic review [Saarto et al., *Cochrane Database System Rev*. 2005; (3):CD005454] addressed the use of antidepressants for the treatment of neuropathic pain in adult patients. The review included 50 trials of 29 antidepressants (total n=2515). The overall conclusion supported efficacy of TCAs for neuropathic pain, with amitriptyline having a number-needed-to-treat of 2 (95% CI 1.7-2.5) and a relative risk of 4.1 (95% CI 2.9-5.9) for obtaining at least moderate relief of pain. Researchers found limited evidence for the efficacy of SSRIs, and insufficient evidence for other antidepressants, including venlafaxine.

In addition to antidepressants, a number of anticonvulsants are used to treat DPNP. After excluding non-diabetic etiologies and stabilizing glycemic control, the American Diabetes Association advises starting treatment of DPNP with a TCA, (e.g., amitriptyline 25-150 mg at bedtime), or an anticonvulsant (e.g., gabapentin 1800 mg daily) [Boulton et al. *Diabetes Care* 2005; 28:956].

Duloxetine is FDA-approved for the treatment of DPNP. Safety and efficacy of duloxetine for the treatment of DPNP were established in two 12-week randomized controlled studies (total n=1074), one of which is published [Goldstein et al. *Pain* 2005; 116(1-2):109-18.]. Based on the published trial, the percent of patients achieving a $\geq$ 50% reduction in 24h Average Pain Score was 49% for patients receiving duloxetine 60 mg/d and 52% with 120 mg/d, compared to 26% of patients receiving placebo. The 60 mg/d dose of duloxetine was better tolerated.

Venlafaxine also appears to be efficacious and safe in DPNP. Rowbotham et al. [*Pain* 2004; 110:697-706] evaluated low dose (75mg) and high dose venlafaxine (150-225 mg) versus placebo in patients with painful diabetic neuropathy. The multicenter, double blind, randomized, placebo-controlled study included 244 adult outpatients with stable type 1 or 2 diabetes. At week 6, the percentage of patients achieving a 50% reduction in Visual Analog Pain Intensity score from baseline was 27% for placebo, 32% for 75mg, and 50% for 150-225mg, $p<0.001$ v. placebo.

Overall, there is insufficient evidence to determine the relative effectiveness of TCAs, SNRIs, or anticonvulsants for the treatment of DPNP or non-diabetic neuropathic pain. The AD1s and the newly introduced anticonvulsant pregabalin are not yet

represented in clinical practice guidelines for DPNP and comparative evidence versus more established therapies is largely unavailable.

ii. Other Non-Psychiatric Conditions

The Committee did not attempt to review all non-psychiatric conditions in which one or more of the AD1s may have a beneficial effect. Some of these apply only to very limited populations (e.g., neurocardiogenic syncope/recurrent idiopathic dizziness), to predictably exploit side effects of the medications (e.g., treatment of premature ejaculation with SSRIs), or to be only an additional option among multiple possible options (e.g., migraine prophylaxis). The Committee noted the following:

- Duloxetine is approved for the treatment of stress urinary incontinence in Europe, under the name of Yentreve. The manufacturer of duloxetine has rescinded its new drug application for U.S. approval for stress urinary incontinence (SUI). It is unclear whether clinical evidence was felt to be insufficient, or whether the FDA is further investigating reports of suicide attempts and suicidal ideation occurring during clinical trials of duloxetine for SUI. The FDA's information sheet on duloxetine currently suggests that physicians consider the data on suicidality before prescribing duloxetine for SUI. Increases in suicidality have not been reported in trials of duloxetine for depression or DPNP.
- There are several clinical trials assessing use of AD1s for the treatment of hot flashes, of particular interest because of the scarcity of effective options for women unwilling or unable to take estrogens. Short-term trials with several AD1s, including venlafaxine, paroxetine, and fluoxetine, have shown efficacy; however, a 9-month, placebo-controlled trial with citalopram and fluoxetine failed to show a significant decrease in hot flashes with either medication, compared with placebo. There are insufficient data to support greater efficacy for any one AD1.
- Duloxetine was shown to be efficacious for the treatment of fibromyalgia in female patients with or without MDD in a 10-week, randomized, double-blind, placebo-controlled trial [Arnold et al., *Am J Med* 2002; 112:191-7], based on significantly greater improvement with duloxetine on the Fibromyalgia Impact Questionnaire (FIQ) total score (mean difference -5.5 points; score range 0-80, 0 = no impact). Response rates, based on patients achieving a $\geq$ 50% reduction in FIQ pain score (score range 0-10, 0 = no impact), were 28% for duloxetine vs. 17% for placebo (p=0.06).

Efficacy / Clinical Outcome Conclusion: The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children.

The Committee noted that efficacy in other psychiatric conditions (GAD, OCD, PD, PMDD, PTSD, SAD, and bulimia) contributes to the overall usefulness of the AD1s. The Committee agreed that the existence of published clinical evidence supporting efficacy in these disease states should be taken into account in addition to FDA-approved indications. By this measure, paroxetine and sertraline appear to be the most broadly useful SSRIs. Bupropion, mirtazapine, trazodone, and nefazodone are indicated only for MDD. With regard to the SNRIs, venlafaxine has FDA-approved indications for GAD and SAD, in addition to MDD.

Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP. It is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.

3) Provider Opinion

The Committee reviewed results of a survey sent to the Army, Navy, and Air Force specialty consultants, and distributed by them to MTF internal medicine, family practice, and psychiatry providers. The survey was also posted on the PEC's webforum, RxNet, to facilitate discussion. Providers were asked to identify clinical situations and differences in safety and tolerability among agents that would lead them to favor one antidepressant over another, and which antidepressants they rarely prescribed and could theoretically live without.

Of 42 responses, 21 were from psychiatrists and 21 from primary care practitioners including internal medicine and family practice. Overall, providers agreed that SSRIs as a class were more useful than SNRIs, followed by bupropion, trazodone, and mirtazapine.

Providers found sertraline to be most useful, followed by escitalopram, fluoxetine, citalopram, paroxetine, and fluvoxamine. About half of the responders perceived escitalopram to offer an efficacy or tolerability advantage over citalopram; the other half saw little or no difference. Provider comments indicated definite niches in therapy for sertraline (many indications; lower risk of adverse effects and drug interactions); fluoxetine (can be used in children, activating); venlafaxine (may be more effective than SSRIs but also has more adverse effects); bupropion (low risk of sexual adverse effects, can be used to treat sexual adverse effects from SSRIs; may be useful in smokers and ADHD patients); trazodone (treatment of sleep symptoms); and mirtazapine (sedating; may be useful to stimulate weight gain in elderly or oncology patients or in HIV wasting).

4) Overall Clinical Effectiveness Conclusion

- The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children. With respect to other psychiatric conditions, paroxetine and sertraline appear to be the most broadly useful AD1s based on FDA-approved indications and published clinical evidence. Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP; it is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.
- The Committee concluded that adverse effects differ across AD1s, but there are little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. The difference in adverse effects between agents may affect the choice of agent in individual patients, creates specific niches in which adverse effects become useful therapeutic effects (e.g., mirtazapine), and increases the number of AD1s necessary to provide adequate clinical coverage.
- Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. Fluvoxamine, fluoxetine, paroxetine, and duloxetine have a generally higher potential for drug interactions than

citalopram, escitalopram, sertraline, and venlafaxine. The likelihood of discontinuation syndrome with the SSRIs appears to correlate with half-life. Venlafaxine may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar, although data are lacking. Discontinuation symptoms appear to be rare with bupropion, which has little serotonergic effect.

- Rare but serious adverse effects include recent case reports of hepatotoxicity with duloxetine, increased seizure risk with bupropion, hepatotoxicity with nefazodone, agranulocytosis with mirtazapine, and priapism with trazodone. Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk). All AD1s are Pregnancy Category C except for bupropion, which is Pregnancy Category B.

COMMITTEE ACTION: The Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. AD1 UF Relative Cost Effectiveness. The P&T Committee evaluated the relative cost effectiveness of the AD1s in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

To determine the relative cost effectiveness of the AD1s, two separate economic analyses were performed a pharmacoeconomic analysis and BIA. From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that AD1s differed in regards to efficacy, safety, and tolerability in the treatment of MDD and other psychiatric illness. To account for the difference in relative clinical effectiveness in this therapeutic class, two cost effectiveness analyses (CEAs) were performed a CEA based on the results obtained via a multi-attribute utility theory (MAUT) analysis, and a CEA based on the findings reported in *Drug Class Review on Second Generation Antidepressants* by the Oregon Health & Science University Drug Effectiveness Review Project (OHSU-DERP). In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). In both CEAs, the drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service).

The CEA-MAUT was presented first. For this analysis, the effectiveness measure used for each agent was the composite score derived from the MAUT analysis that ranked the agents based on clinical outcome evidence. The MAUT accounted for the differences in clinical outcome evidence; FDA indication supporting an agent's use for psychiatric and non-psychiatric conditions other than MDD, such as GAD, PTSD, DPNP, etc.; evidence supporting efficacy and safety in the pediatric population; differences in safety (e.g., drug interactions, use in pregnancy, contraindications, potential for cardiovascular adverse events, and potential for rare but serious adverse events); and differences in tolerability (e.g., sexual dysfunction).

Overall, the results of the CEA-MAUT were as follows:

- Trazodone was determined to be the most cost-effective agent;
- Fluoxetine and sertraline were determined to be more cost effective and more costly compared to trazodone;

- Other agents were shown to be less effective and more costly, compared to trazodone, fluoxetine, and sertraline.

With respect to the SSRIs:

- Fluoxetine was most-effective, followed by citalopram, paroxetine IR, escitalopram, and paroxetine CR, in that order.

With respect to the SNRIs:

- Venlafaxine was shown to be more cost-effective compared to duloxetine.

With respect to the other AD1s:

- Trazodone was the most cost effective agent followed by mirtazapine, nefazodone, bupropion SR, and bupropion XL, in that order.
- (Note: Although trazodone was determined to be the most cost-effective agent, and nefazodone was shown to be more cost-effective compared to bupropion SR and bupropion XL, neither trazodone nor nefazodone was considered a viable first-line monotherapy treatment alternative for MDD).

The second cost effectiveness analysis (CEA-Response) was based on the OHSU-DERP report for MDD. This report examined 49 head-to-head randomized controlled clinical trials and one systematic review. The overall conclusion of the report was that "effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs. Studies were often small and relatively underpowered to detect significant differences in efficacy." However, both the OHSU-DERP report and the PEC clinical review did acknowledge that there was some evidence to suggest that escitalopram is more effective compared to citalopram; venlafaxine has a modest but statistically significant additional treatment effect compared to fluoxetine; and that escitalopram and venlafaxine are equally effective. However, one of two studies reported significantly greater discontinuations due to adverse effects in the venlafaxine group than in the escitalopram group. To account for these potential differences in clinical outcomes, a CEA-Response model was constructed. This model examined the costs and outcomes of treatment for MDD during the acute phase of treatment (8-weeks). In addition to drug costs, other direct medical costs included provider costs and costs associated with the treatment of adverse events. The effectiveness measure was reported response rate at 8-weeks.

Overall, the results from the CEA-Response analysis revealed that:

- Fluoxetine was the most cost-effective agent;
- Escitalopram was more effective and more costly;
- Venlafaxine was equivalent in effectiveness compared to escitalopram, but was significantly more costly;
- Other agents were equivalent in effectiveness compared to fluoxetine but were more costly.

A summary analysis was then conducted based on the CEA-MAUT and CEA-Response results. The summary analysis focused on comparisons either between the most cost-effective agent and

the more costly agents within a sub-class or between a generic agent and its branded product extension (e.g., paroxetine IR and paroxetine CR). This analysis focused on the:

- SSRIs – fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), sertraline, escitalopram, and paroxetine CR;
- SNRIs – venlafaxine versus duloxetine;
- Bupropion XL versus Bupropion SR.

The results of the summary analysis showed:

For the SSRIs:

- Fluoxetine branded product extensions - Sarafem and Prozac Weekly were > 7-fold more costly and had similar relative clinical effectiveness compared to generic fluoxetine;
- Sertraline had equal (CEA-Response) or slightly greater (CEA-MAUT) relative clinical effectiveness but was significantly more costly compared to fluoxetine;
    - (Note. sertraline is projected to go generic in June 2006)
- Escitalopram was shown to have lower overall relative clinical effectiveness (CEA-MAUT) compared to fluoxetine but potentially greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to citalopram, however at a significantly greater cost;
- The CEA-MAUT and CEA-Response both showed the paroxetine IR and paroxetine CR had similar relative clinical effectiveness, but paroxetine CR was significantly more costly compared to paroxetine IR.

For the SNRIs:

- Venlafaxine was shown to have greater overall relative clinical effectiveness (CEA-MAUT) and greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to duloxetine for a similar cost;
- Bupropion XL was shown to have greater overall relative clinical effectiveness (CEA-MAUT) but similar relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to bupropion SR at a significantly greater cost.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of AD1s best meets the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical considerations (e.g., the need to make a broad array of antidepressants available to meet the clinical coverage needs), the Committee agreed that a group of AD1s that included bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine IR, sertraline, trazodone, and venlafaxine best achieved this goal when compared to other combination groups of AD1s, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (12 for, 5 opposed, 1 abstention, 1 absent) to accept the AD1 cost-analysis presented by the PEC. The P&T Committee concluded that: fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), escitalopram, and paroxetine CR were not cost-effective relative to the other agents within the SSRI sub-class; duloxetine was not cost-effective compared to venlafaxine; bupropion XL was not cost-effective compared to bupropion. Ultimately, the P&T committee did not value escitalopram's potentially greater relative clinical effectiveness in the treatment of MDD (based on clinical trial evidence supporting a clinical efficacy advantage over citalopram) or bupropion XL's greater overall relative clinical effectiveness (based on its once-daily dosing regimen) enough to overcome the agents' significantly higher cost. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the AD1s, and other relevant factors, the P&T Committee recommended that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF and that bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine (HCl and mesylate formulations), sertraline, trazodone, venlafaxine and venlafaxine extended release be classified as formulary on the UF. The P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued, since there is little new information to support the safety and efficacy of weekly doses exceeding 90 mg.

COMMITTEE ACTION. The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstention, 1 absent) to recommend that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly) escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine and venlafaxine extended release remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued.

C. AD1 UF Medical Necessity Criteria: Based on the clinical evaluation of the AD1s and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1.) Use of formulary agents is contraindicated, and the use of a non-formulary agent is not contraindicated.

2). The patient has experienced or is likely to experience significant adverse effects from the formulary agents, and the patient is reasonably expected to tolerate a non-formulary agent.

3) Use of the formulary agent resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary agent.

4) The patient has previously responded to a non-formulary agent and changing to a formulary agent would incur unacceptable risk.

5) There is no alternative pharmaceutical agent on the formulary.

With respect to criteria 2 and 3, the Committee noted the following:

Adverse effect profiles are known to differ among the AD1s and other factors may play a part in selecting an agent for a particular patient (e.g., symptoms of sedation or agitation, family history of efficacy). Clinical practice guidelines support SSRIs as the first choice in most patients, and support trying a second SSRI in patients who have failed a first SSRI due to lack of efficacy, but they do not support trying all available SSRIs before being treated with an antidepressant with a different mechanism of action.

- For escitalopram, the Committee supported medical necessity in the following cases:
  - The patient has previously failed adequate trials of at least two other SSRIs (at least 8 weeks each), without response or remission, and other formulary medications (such as venlafaxine and bupropion) are not appropriate for treatment.
  - The patient has previously tried at least two other SSRIs and could not tolerate the adverse effects, and other formulary medications (such as venlafaxine and bupropion) are not appropriate for treatment.
- For duloxetine, the Committee supported medical necessity in patients who have tried and failed, or were unable to tolerate, venlafaxine, and in whom other formulary medications (e.g., SSRIs and bupropion) are not appropriate for treatment.
- The Committee had difficulty envisioning circumstances in which paroxetine controlled release (Paxil CR), bupropion extended release (Wellbutrin XL), fluoxetine 90 mg extended release capsules (Prozac Weekly), and specially packaged fluoxetine for PMDD (Sarafem) would be considered medically necessary, since all of these medications would be available on the UF in other formulations. With respect to paroxetine CR, which has data supporting a significantly lower incidence of nausea in the first week after starting therapy compared to the IR formulation, the Committee agreed that one circumstance in which paroxetine CR could be considered medically necessary might be in a patient who had previously responded to paroxetine and who had other predisposing factors for nausea (e.g., chemotherapy or a GI disorder).

With respect to criterion 5, the Committee agreed that medical necessity criteria for duloxetine in DPNP should be based on national clinical practice guideline recommendations for treatment of DPNP. The Committee also agreed that duloxetine could be considered medically necessary in other types of neuropathic pain (e.g., phantom limb syndrome) under criterion #5 if reliable evidence exists for safety and efficacy and more accepted therapies are not clinically appropriate.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 abstained, 2 absent) to accept the AD1s medical necessity criteria.

D. AD1 UF Implementation Plan: Because a substantial number of patients is currently receiving non-formulary AD1s and the need to carefully assess and monitor patients taking this class of medication, the P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 abstained, 2 absent) to recommend an implementation period of 180 days.

E. AD1 Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the AD1s recommended for inclusion on the UF to select recommended

agents for the BCF. Based on the outcome of relative clinical effectiveness determinations, the Committee decided that three or four SSRIs, zero or one SNRIs, and zero to two other agents (bupropion, mirtazapine, nefazodone, or trazodone) would be added to the BCF. AD1s currently on the BCF include: citalopram, fluoxetine (excluding Sarafem and Prozac Weekly), paroxetine (excluding Paxil CR), sertraline, venlafaxine extended release, bupropion sustained release (but not Wellbutrin XL), and trazodone.

With respect to the SSRIs, the Committee agreed that it was reasonable to add fluoxetine (excluding Prozac Weekly and Sarafem) and citalopram to the BCF, based on cost effectiveness and clinical effectiveness considerations. In addition, the Committee agreed that sertraline should be added to the BCF despite its significantly higher cost compared to fluoxetine and citalopram. Sertraline is the most commonly used SSRI in MTFs and its relative clinical effectiveness based on the CEA-MAUT was slightly greater than other SSRIs, primarily as a result of its FDA-approved indications and evidence supporting efficacy in a large number of psychiatric conditions in addition to MDD, as well as its relatively low risk of drug interactions and adverse effects. Sertraline is expected to become generically available in June of 2006. Given the inclusion of fluoxetine, citalopram, and sertraline, the Committee agreed that paroxetine IR should not be added to the BCF. Reasons for not adding paroxetine to the BCF include: 1) it's not as cost effective as fluoxetine and citalopram, 2) it has declining use in MTFs, 3) it was ranked lower by providers compared to other SSRIs, 4) it has a relatively high risk of drug interactions and adverse effects, 5) a high risk of discontinuation syndrome; and 6) a recent labeling change regarding use in pregnancy.

With respect to the SNRIs, the Committee concluded that venlafaxine should not be added to the BCF. Although venlafaxine may be slightly more efficacious than SSRIs, it is also associated with more adverse effects, including the potential for increases in blood pressure. It is typically not used for initial treatment. The cost of venlafaxine is at least two-fold higher than treatment with any SSRI and several times higher than treatment with the most cost-effective SSRI. While SNRIs have a definite place in therapy, the Committee agreed that it was not necessary to retain an SNRI on the BCF.

With respect to the other AD1s, the Committee agreed that trazodone and bupropion sustained release should be added to the BCF. Trazodone is relatively commonly used in MTFs (about 12,000 prescriptions per month), is available at low cost, and its use as an adjunctive medication for insomnia in depressed patients was supported by provider opinion. Bupropion sustained release is also commonly used in MTFs, and has a definite and well-supported role in treatment of patients who have experienced or are concerned about sexual dysfunction with SSRIs.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend the following as the BCF agents: fluoxetine (excluding Prozac Weekly and Sarafem, which are non-formulary), citalopram, sertraline, trazodone, and bupropion SR**.**

12. MACROLIDES/KETOLIDE DRUG CLASS REVIEW

A. Macrolide/Ketolide Relative Clinical Effectiveness: The DoD P&T Committee evaluated the relative clinical effectiveness of the macrolides: azithromycin (Zithromax), azithromycin 2 gram extended release suspension (Zmax), clarithromycin IR (Biaxin and various generics), clarithromycin extended release (ER) (Biaxin XL), all erythromycin salts and esters as well as erythromycin/sulfisoxazole combination suspension (various generics); and the ketolide, telithromycin (Ketek). Information regarding the safety, effectiveness, and clinical outcomes

for the treatment of various infections was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21.

1) Spectrum of Activity/Resistance: Increasing use of macrolides has resulted in increased rates of macrolide resistant *S. pneumoniae.* Macrolide resistance to *S. pneumoniae* appears to be a class effect. *In-vitro*, telithromycin remains active against macrolide and penicillin resistant *Streptococcus*, and is the only agent in the class with an FDA indication for multi-drug resistant *S. pneumoniae* (MDRSP). However, telithromycin's ability to overcome MDRSP has not resulted in higher cure rates. *H. influenzae* is commonly resistant to erythromycin, whereas azithromycin, clarithromycin and telithromycin are active against *H. influenzae*

2) Efficacy

a) Endpoints: Endpoints in the clinical trials included clinical cure rate, bacteriologic eradication, and antibiotic failure rates. Any applicable trials evaluating clinical outcomes, such as mortality, hospital admission rates, or length of hospitalization, were also evaluated.

b) Efficacy for Community Acquired Pneumonia (CAP)

Place in Therapy: The American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Canadian Infectious Diseases Society/Canadian Thoracic Society (CIDS/CTS) guidelines do not give a preference for azithromycin or clarithromycin for treating CAP, but state that erythromycin is not preferred due to poor tolerability and limited spectrum of activity. There are no specific recommendations yet for telithromycin, although an update in ATS/IDSA guidelines is expected soon.

Efficacy of Macrolides/Ketolide: The Committee reviewed 17 head-to-head trials comparing one macrolide/telithromycin to another macrolide/telithromycin, or one macrolide/telithromycin versus another antimicrobial agent. Sixteen trials showed similar cure rates and/or bacteriological eradication rates. One poor quality trial comparing azithromycin to clarithromycin found a significant decrease in length of hospitalization and mortality with azithromycin. Another trial examined healthcare utilization from two pooled trials comparing clarithromycin IR to telithromycin. Despite equivalent cure rates in the individual trials, telithromycin was associated with significantly fewer CAP-related hospitalizations than clarithromycin IR in the pooled analysis. The original studies in the pooled analysis were not designed to analyze healthcare utilization; therefore, results were interpreted with caution.

CAP Conclusion: The Committee concluded there was no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating CAP. Erythromycin may have limited clinical utility in treating CAP caused by *H. influenzae,* due to its inactivity against the microorganism.

c) Efficacy for Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB):

Place in Therapy: Guidelines from the American College of Physicians (ACP), American Society of Internal Medicine (ASIM), and American College of Chest Physicians do not give specific recommendations for the treatment of ABECB. Other recommendations from noted infectious disease physicians state azithromycin and clarithromycin are recommended in patients with uncomplicated ABECB (< 65 years of age; < 4 exacerbation per year, no co-morbidities, and minimal or no impairment in pulmonary function). Erythromycin was not recommended due to limited activity

against *H. influenzae.* No guidelines or recommendations have addressed the use of telithromycin for ABECB.

Efficacy of Macrolides/Ketolide: The Committee reviewed six double-blind, head-to-head trials comparing one macrolide/telithromycin to another macrolide, or another antimicrobial agent. All six trials showed similar cure rates and/or bacteriological eradication rates for the treatment of ABECB. One trial evaluated healthcare utilization, and found telithromycin was associated with significantly fewer respiratory-related hospitalizations, all-cause hospitalizations, and emergency room visits than clarithromycin IR, despite similar clinical cure rates. Healthcare utilization was a secondary endpoint to this study, and results should be interpreted with caution.

ABECB Conclusions: The Committee concluded there is no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating ABECB. Erythromycin may have limited clinical utility in treating ABECB caused by *H. influenzae,* due to its inactivity against the microorganism

d) Efficacy for Acute Bacterial Sinusitis (ABS):

Place in Therapy: Treatment guidelines from the American Academy of Pediatrics (AAP) and the Sinus and Allergy Health Partnership (SAHP) recommend clarithromycin and azithromycin in patients with mild uncomplicated ABS who have a type I hypersensitivity to penicillin. The AAP guidelines no longer recommend erythromycin for ABS due to the increasing resistance. However, the SAHP guidelines do not give preference to any macrolide, and include telithromycin in the same treatment category as the other macrolides for ABS.

Efficacy of Macrolides/Ketolides: Six double-blind, head-to-head trials comparing a macrolide/telithromycin to another macrolide or another antimicrobial showed similar cure rates and/or bacteriological eradication rates for the treatment of ABS. A retrospective cohort study of 29,102 patients with ABS concluded that newer broad spectrum antibiotics (azithromycin clarithromycin and amoxicillin-clavulanate) were no better than amoxicillin, trimethoprim-sulfamethoxazole, or erythromycin.

ABS Conclusions: The Committee agreed that all the macrolides (azithromycin, Zmax, clarithromycin IR/ER, and erythromycin) and telithromycin have shown efficacy for the treatment of ABS, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products when treating ABS.

e) Efficacy for Acute Pharyngitis:

Place in Therapy: The IDSA guidelines and a position paper by the ACP/ASIM for the treatment of group A β-hemolytic streptococcus pharyngitis (GABHS) recommend erythromycin only in patients with a history of a penicillin allergy. Erythromycin is recommended due to its narrow spectrum of activity compared to azithromycin and clarithromycin. Azithromycin, clarithromycin, or telithromycin are recommended in patients who cannot tolerate erythromycin.

Efficacy of Macrolides/Ketolide: Three trials comparing clarithromycin IR to azithromycin or telithromycin, as well as one trial comparing azithromycin to erythromycin showed similar clinical cure rates. Six trials comparing all the products,

(except Zmax, which has not been studied) have shown similar cure rates to penicillin, the gold standard for the initial treatment of acute pharyngitis.

Acute Pharyngitis Conclusions: The Committee agreed that azithromycin, clarithromycin IR/ER, erythromycin, and telithromycin have shown efficacy for the treatment of pharyngitis, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Currently there are no published trials evaluating Zmax for the treatment of acute pharyngitis.

f) Efficacy for Acute Otitis Media (AOM):

Place in Therapy. *T*he AAP and the American Academy of Family Physicians (AAFP) guidelines recommended macrolides as third-line agents, with use reserved for patients with a history of a type I reaction to penicillins and cephalosporins. The guidelines state that azithromycin, clarithromycin, and erythromycin/sulfisoxazole are all considered preferred macrolides. Erythromycin alone is not recommended due to its lack or activity against *H. influenzae*.

Efficacy of Macrolides: Two head-to-head trials comparing azithromycin to clarithromycin showed similar clinical cure rates. In addition, trials comparing azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin to either standard dose amoxicillin or amoxicillin-clavulanate showed similar cure rates. There were no clinical trials found evaluating clarithromycin ER, Zmax, and telithromycin for the treatment of AOM, and these agents do not have an FDA indication for the treatment of AOM.

AOM Conclusions: The Committee agreed that azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin have shown efficacy against AOM versus amoxicillin or amoxicillin-clavulanate, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Erythromycin alone may not be as effective for AOM compared to the other macrolides due to its inactivity against *H. influenzae*. There were no clinical trials found evaluating clarithromycin ER, Zmax and telithromycin for the treatment of AOM.

g) Efficacy for H. pylori infections and Mycobacterium avium complex (MAC):

Macrolides/ketolides are also used to treat infections cause by mycobacterium avium complex in the immunocompromised population and *H. pylori*-associated peptic ulcer disease. These infections occur with less frequency in DoD than respiratory infections. Thus, the Committee briefly reviewed the data and concluded the following: 1) For *H. pylori* eradication, clarithromycin-based regimens appear to be superior to azithromycin-based regimens; and 2) other macrolide/ketolides have not been adequately evaluated. For the prevention of MAC, either azithromycin or clarithromycin IR is recommended; there is insufficient data from the other macrolides/ketolides to recommend their use. For treatment of MAC, clarithromycin IR may be superior to azithromycin at clearing MAC from the blood, but trials have shown no mortality difference between the two drugs.

3) Safety and Tolerability:

Rare but Serious Adverse Drug Reactions (ADRs): All the macrolides/ketolides have the propensity, based on case reports and clinical trials, to cause pseudomembranous colitis, hepatotoxicity, and to prolong the QTc interval. Erythromycin and telithromycin

may cause exacerbation of myasthenia gravis, and should be used with caution in these patients.

Other ADRs: All the macrolide/ketolide products can cause taste perversion/abnormal taste, dizziness, rash, headache, and transient hearing loss. Cases of visual disturbances have been reported with telithromycin.

GI ADRs: Erythromycin has the highest incidence of GI adverse effects (abdominal pain, diarrhea, nausea/vomiting) compared to the other products. Package insert data suggest that Zmax and telithromycin cause more GI related adverse effects than clarithromycin IR/ER or azithromycin.

Special Populations. Pregnancy and Pediatric: Azithromycin and erythromycin are rated pregnancy category B rating whereas clarithromycin and telithromycin are rated pregnancy category C. Azithromycin, clarithromycin IR, and erythromycin are the only agents that have been evaluated in pediatric patients.

Drug Interactions: Azithromycin and Zmax are not metabolized via hepatic cytochrome P450 3A4 mechanisms, and are associated with fewer drug interactions than clarithromycin IR/ER, erythromycin, or telithromycin.

Overall Safety and Tolerability Conclusion: The Committee concluded that azithromycin and Zmax have the most favorable safety/tolerability profile, followed by clarithromycin and telithromycin, with erythromycin having the least favorable safety/tolerability profile.

4) Other Factors:

Pharmacokinetics: Erythromycin stearate and base need to be given on an empty stomach, whereas erythromycin ethylsuccinate and estolate can be given without regard to meals. Zmax bioavailability increases greater than two-fold when administered with food, but should be given on an empty stomach due the possibility of increasing the risk of adverse effects. Azithromycin, clarithromycin and telithromycin can be given without regard to meals. Azithromycin and Zmax are not interchangeable, due to differences in absorption and the time to reach peak serum concentration. Both clarithromycin and telithromycin require dosage adjustment for renal dysfunction; telithromycin requires dosage adjustment for liver dysfunction with concomitant renal dysfunction.

Dosing: The following agents can be given daily. Azithromycin, clarithromycin ER, and telithromycin. Clarithromycin IR is dosed twice daily, whereas erythromycin can be dosed between two to four times daily. Zmax is the only agent that is administered as a one-time dose.

Palatability of Oral Suspensions: Clinical studies evaluating taste preferences of antibiotic suspensions showed that pediatric patients preferred the taste of azithromycin over clarithromycin or erythromycin/sulfisoxazole.

Provider Opinion: A survey of DoD providers revealed that MDRSP was not considered a problem when treating CAP in the outpatient setting; there was not an advantage of Zmax's one time dosing versus other azithromycin products; azithromycin was preferred over the other agents in the class; and telithromycin and Zmax were thought to confer no additional benefit over the other members in the drug class.

Conclusions for Other Factors: There are minor differences in the pharmacokinetic profiles, dosing frequency, and palatability of the macrolides/ketolides that can affect individual patient preferences.

Overall Clinical Effectiveness Conclusion: The Committee concluded: (1) telithromycin *in vitro* shows activity against MDRSP, but this has not translated into superior clinical cure/improvement/bacteriological eradication rates in clinical trials; (2) erythromycin may have a limited role in treating many common types of upper and lower respiratory tract infections due to inactivity against *H. influenzae*; (3) clinical cure rates/bacterial eradication rates are similar between the macrolides/ketolides when used for treating CAP, ABECB, ABS, and acute pharyngitis; (4) for AOM, there is no clinical trial experience with clarithromycin ER or Zmax; clinical cure rates are similar with the other products; (5) clarithromycin IR has the best evidence for the treatment of *H. pylori* infections; (6) either azithromycin or clarithromycin can be used for prevention of MAC infection and clarithromycin IR is preferred over azithromycin for the treatment of MAC infections; (7) azithromycin is preferred relative to other macrolides and telithromycin in terms of safety and tolerability; and (8) there are minor differences amongst the agents in terms of other factors. Overall, the Committee concluded that azithromycin has increased overall clinical effectiveness relative to Zmax, clarithromycin IR/ER, erythromycin, and telithromycin.

COMMITTEE ACTION: The DoD P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. **Macrolide Antibiotic UF Relative Cost Effectiveness:** In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 C.F.R. 199.21(e)(2).

The macrolide cost effectiveness review was conducted as two discreet analyses. The first analysis considered only the erythromycin salts and base, while the second analysis compared the newer macrolides [azithromycin, Zmax (brand), clarithromycin, and telithromycin]. The first step for each evaluation utilized a cost-analysis to calculate the total weighted average cost per course of therapy for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review suggested minimal differences in clinical effectiveness (efficacy, safety, and tolerability) between the erythromycin salts and base, the appropriate pharmacoeconomic analysis for these agents was determined to be cost-minimization. However, a CEA was used to evaluate Zmax, azithromycin, clarithromycin, and telithromycin, because the clinical review suggested differences in clinical effectiveness (efficacy, safety, and tolerability) between these agents. Effectiveness differences between the agents were quantified through the use of a MAUT table.

Although the results of the erythromycin cost analysis (salts and base) determined erythromycin base to have the lowest total weighted average cost per course of therapy across all points of service (MTF, TRRx, TMOP), the cost effectiveness profiles for all the erythromycin agents were considered favorable.

The cost-analysis evaluation between azithromycin, Zmax, clarithromycin, and telithromycin determined azithromycin to have the lowest total weighted average cost per course of therapy across all points of service, followed by Zmax, clarithromycin, and telithromycin, respectively.

The CEA produced results with the same rank order, i.e, azithromycin being the most cost-effective followed by Zmax, clarithromycin and telithromycin.

The results of the above analyses were then incorporated into a BIA, which accounted for other factors and costs associated with a potential decision regarding formulary status of macrolide antibiotics within the UF. These factors included market share migration (due to changing provider prescribing practices), cost reduction associated with non-formulary status, and medical necessity processing fees. Switch costs were not included, because the macrolides were assumed to be used acutely rather than on a chronic basis. The results of the BIA confirmed the results of the preliminary analyses. Erythromycin and azithromycin (other than the Z-max formulation) were found to be the most cost-effective macrolide antibiotics overall. A sensitivity analysis conducted around the uncertainty of azithromycin prices due to its generic availability suggested that, as the price of generic azithromycin falls: 1), azithromycin becomes even more cost effective compared to other second generation macrolides; and 2) scenarios placing the branded Z-max formulation into the non-formulary tier become increasingly more cost beneficial to DoD.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative-cost effectiveness analyses presented for the macrolide antibiotics. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the macrolide antibiotics, the P&T Committee recommended that the status of telithromycin and the Zmax formulation of azithromycin be changed from formulary to non-formulary on the UF, with erythromycin (base and salts), clarithromycin immediate and extended release, and non-Zmax formulations of azithromycin maintaining formulary status on the UF with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend non-formulary status on the UF for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin, and non-Zmax formulations of azithromycin maintaining formulary status on the UF at the formulary cost share.

C. Macrolide/Ketolide UF Medical Necessity Criteria: Based on the clinical evaluation of macrolides and telithromycin and the conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of a formulary macrolide (azithromycin, clarithromycin IR/ER, and erythromycin) is contraindicated, and the use of a non-formulary agent (Zmax and telithromycin) is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary macrolides, and the patient is reasonably expected to tolerate a non-formulary agent.

3) Treatment with a formulary macrolide has resulted in a therapeutic failure, and the patient is reasonably expected to respond to a non-formulary agent. [Note: “Therapeutic failure” to be outlined on the medical necessity form].

4) There is no alternative formulary agent available. The patient may receive telithromycin if he/she has a recent history of documented MDRS, and cannot be treated with agents from other formulary antibiotic classes (e.g., quinolone antibiotics).

COMMITTEE ACTION: The DoD P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the macrolide/ketolide medical necessity criteria.

D. Macrolide/ketolide UF: Because of the low utilization of Zmax and telithromycin at the MTFs, and the fact that these agents, for the most part, are not used chronically, the Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend an implementation period of 60 days.

E. Macrolide/Ketolide BCF Review and Recommendations: The P&T Committee reviewed the macrolides recommended for inclusion on the UF to select the BCF macrolide.

There are currently two macrolides on the BCF: azithromycin 250 mg tablet, and all formulations of erythromycin with the exception of erythromycin particles in tablets (PCE Dispertab) and erythromycin base delayed release capsule. From a clinical and economic standpoint, azithromycin 250 mg tablets and at least one erythromycin salt/ester are rational selections for the BCF. Azithromycin is the highest utilized macrolide in the entire MHS (MTF, TRRx, and TMOP), has a wide range of FDA indications, and is now generically available. Erythromycin has a wide variety of FDA indications, is efficacious for many different types of infections, has a niche in the treatment certain types of disorders/infections, is relatively low in cost compared to the other macrolides and telithromycin, and is generically available. Because of the large number of erythromycin formulations (base and salts), and no one erythromycin formulation has shown to have superior clinical efficacy over another, the individual MTFs can decide what erythromycin formulation should be added to their local formulary.

Conclusion: The Committee concurred with the recommendation to place azithromycin 250 mg tablet and one erythromycin salt/ester on the BCF.

COMMITTEE ACTION: The DoD P&T Committed voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend azithromycin 250 mg tablet, and one erythromycin (base or salt) as the BCF agent(s).

13. ANTI-MUSCARINIC OVER ACTIVEBLADDER MEDICATIONS

PEC staff presented a clinical review of the medications used for the treatment of overactive bladder disease. The agents in this class include oxybutynin chloride immediate release (Ditropan), extended release (Ditropan XL), and transdermal patches (Oxytrol); tolterodine tartrate immediate release (Detrol) and extended release (Detrol LA); trospium chloride (Sanctura); solifenacin succinate (VESIcare); and darifenacin hydrobromide (Enablex). The current BCF agents for this class are oxybutynin chloride immediate release and tolterodine tartrate extended release (Detrol LA). The BCF specifically excludes oxybutynin chloride extended release (Ditropan XL).

The Committee provided expert opinion regarding the key questions in this drug class and clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Both the clinical and cost effectiveness analyses will be completed during the February 2006 meeting; no action necessary.

13. ADJOURNMENT

The third day of the meeting adjourned at 1130 hours on November 18, 2005. The dates of the next meeting are February 14 – 16, 2006.

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Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix A – Table 1. Implementation Status of UF Class Review Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have terazosin and alfuzosin on formulary.
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have the CC formulation of nifedipine ER (Adalat CC or its generic equivalent) verapamil SR, and the Tiazac formulation of diltiazem ER on formulary.
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have captopril, lisinopril, and lisinopril HCTZ on formulary.
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05. MTFs may add vardenafil to formulary based on local needs
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05. MTFs must have nystatin and clotrimazole topical products on formulary.
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05. MTFs must have Avonex on formulary if local needs necessitate having medications in this class on formulary.

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05. MTFs must have telmisartan and telmisartan/HCTZ on formulary.
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05. MTFs must have omeprazole and rabeprazole on formulary.

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy;
TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs Nov 2005 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Pregabalin (Lyrica; Pfizer) capsules; GABA Analogue	Dec 04 (not launched until Sept 05): Lyrica is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Lyrica is indicated as adjunctive therapy for adult patients with partial onset seizures	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Ramelteon tablets (Rozerem; Takeda); Selective melatonin receptor agonist (Non-benzodiazepine sedative hypnotic)	Jul 05 (launched in Sept 05); Ramelteon is indicated for the treatment of both chronic and transient insomnia characterized by difficulty with sleep onset.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Mecasermin injection (Increlex; Tercica Pharmaceuticals); Recombinant human insulin-l-like growth factor-1 (IGF-1)	Aug 05 (anticipated launch in Jan 06); growth deficiency; Mecasermin is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion and have developed neutralizing antibodies to GH.	Prior Authorization recommended due to safety concerns (hypoglycemia) and the potential for misuse in patients with short stature. Consideration of UF status deferred until drug class is reviewed.
Mometasone furoate oral inhaler (Asmanex Twisthaler; Schering Plough); Oral inhaled corticosteroids	Mar 05 (launched in Jul 05); Asmanex Twisthaler is indicated for the maintenance of asthma as prophylactic therapy in patients 12 years of age or older. The Asmanex Twisthaler is also indicated for asthma patients who require oral corticosteroid therapy, where adding Asmanex Twisthaler therapy may reduce or eliminate the need for oral corticosteroids.	Quantity limits recommended due to existing precedence in the class. Consideration of UF status deferred until drug class is reviewed.
Omega 3 acid ethyl esters capsules (Omacor; Reliant Pharmaceuticals); Fish oil supplement	Nov 04 (launched Sep 05); Omacor is indicated as an adjunct to diet to reduce very high (>500 mg/dL) triglyceride levels in adults.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Nepafenac ophthalmic solution 0.1% (Nevanac; Alcon); Ophthalmic NSAID	Aug 05 (launched Sept 05); Nevenac is indicated for the treatment of postoperative inflammation associated with cataract surgery.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – Table 3. Table of Abbreviations

AAP	American Academy of Pediatrics
ABECB	acute bacterial exacerbation of chronic bronchitis
ABS	acute bacterial sinusitis
ACP	American College of Physicians
AD1(s)	Antidepressants-1 (Group of antidepressants considered in Nov 2005 P&T antidepressant review)
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AOM	acute otitis media
ASIM	American Society of Internal Medicine
ATS	American Thoracic Society
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPI	Brief Pain Inventory
CAP	community acquired pneumonia
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CIBIC-Plus	Clinician's Interview Based Assessment of Change - Plus
CIDS/CTS	Canadian Infectious Diseases Society/Canadian Thoracic Society
CMA	cost-minimization analysis
CR	controlled release
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
DPNP	diabetic peripheral neuropathic pain
ECF	Extended Core Formulary
ER	extended release
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GAD	generalized anxiety disorder
GH	growth hormone
GHR	growth hormone receptor
GI	gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
HPA	hypothalamic adrenal axis
IDSA	Infectious Diseases Society of America
IGF	insulin growth factor
IGFD	insulin growth factor-1 deficiency
IR	immediate release
LFT	liver function test
MAC	*M. avium* complex
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxydase inhibitor
MAUT	multi-attribute utility theory
MDD	major depressive disorder
MDRSP	multi-drug resistant *S. pneumoniae*
MHS	Military Health System
MTF	military treatment facility
NDRI	norepinephrine dopamine reuptake inhibitor

NICE	(British) National Institute for Clinical Excellence
NMDA	N-methyl D-aspartate
OCD	pbsessive compulsive disorder
OHSU-DERP	Oregon Health & Science University Drug Effectiveness Review Project
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	perennial allergic rhinitis
PD	panic disorder
PEC	Pharmacoeconomic Center
PMDD	premenstrual dysphoric disorder
PTSD	posttraumatic stress disorder
RA	rheumatoid arthritis
SAD	social anxiety disorder
SAHP	Sinus and Allergy Health Partnership
SAR	seasonal allergic rhinitis
SIB	Severe Impairment Battery
SNRI	serotonin norepinephrine reuptake inhibitor
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
SUI	stress urinary incontinence
TCA	tricyclic antidepressant
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
XR	extended release

AAP	American Academy of Pediatrics
ABECB	acute bacterial exacerbation of chronic bronchitis
ABS	acute bacterial sinusitis
ACP	American College of Physicians
AD1	Antidepressants Group 1 (group of antidepressants considered in the November 2005 P&T antidepressant drug class review – see page 26 for listing)
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AOM	acute otitis media
ASIM	American Society of Internal Medicine
ATS	American Thoracic Society
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
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CCOHTA	Canadian Coordinating Office of Health Technology Assessment
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CIDS/CTS	Canadian Infectious Diseases Society/Canadian Thoracic Society
CMA	cost-minimization analysis
CR	controlled release
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
DPNP	diabetic peripheral neuropathic pain

ECF	Extended Core Formulary
ER	extended release
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GAD	generalized anxiety disorder
GH	growth hormone
GHR	growth hormone receptor
GI	Gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
HPA	hypothalamic adrenal axis
IDSA	Infectious Diseases Society of America
IGF	insulin growth factor
IGFD	insulin growth factor-1 deficiency
IR	immediate release
LFT	liver function test
MAC	*M. avium* complex
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAUT	multi-attribute utility theory
MDD	major depressive disorder
MDRSP	multi-drug resistant *S. pneumoniae*
MHS	Military Health System
MTF	military treatment facility

NDRI	norepinephrine dopamine reuptake inhibitor
NICE	(British) National Institute for Clinical Excellence
NMDA	N-methyl D-aspartate
OCD	obsessive compulsive disorder
OHSU-DERP	Oregon Health & Science University Drug Effectiveness Review Project
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	perennial allergic rhinitis
PD	panic disorder
PEC	Pharmacoeconomic Center
PMDD	premenstrual dysphoric disorder
PTSD	posttraumatic stress disorder
RA	rheumatoid arthritis
SAD	social anxiety disorder
SAHP	Sinus and Allergy Health Partnership
SAR	seasonal allergic rhinitis
SIB	Severe Impairment Battery
SNRI	serotonin norepinephrine reuptake inhibitor
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
SUI	stress urinary incontinence
TCA	tricyclic antidepressant
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
XR	extended release

19 August 2005

DECISION PAPER:

AUGUST 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

5. ITEMS FOR INFORMATION

6. REVIEW OF RECENTLY APPROVED AGENTS

The Committee reviewed one new product in a class previously reviewed for Uniform Formulary (UF) status. Revatio is a new sildenafil product approved for the treatment of pulmonary arterial hypertension (also known as primary pulmonary hypertension). Unlike the other phosphodiesterase-5 inhibitor products (sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)), Revatio is not approved for erectile dysfunction. Cialis and Viagra have been classified as non-formulary under the UF.

***COMMITTEE ACTION*:** The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend that Revatio be added to the UF (see paragraph 6 on page 10 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR PRAMLINTIDE (SYMLIN) INJECTION

The Committee agreed that a PA was needed for pramlintide (Symlin) subcutaneous injection due to safety issues.

***COMMITTEE ACTION*:** Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended (17 for, 0 against, 0 abstained, 0 absent) that PA be required for pramlintide (see paragraph 7 on pages 10 – 11 of P&T Committee minutes for rationale and summary of PA criteria).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

***COMMITTEE ACTION*:** The Committee recommended that the PA for pramlintide should have an effective date no later than the first Wednesday following a 30-day implementation period. In order to avoid interruptions in therapy, the Committee recommended that patients who received pramlintide from a DoD pharmacy point of service prior to the PA effective date should be allowed to continue to receive pramlintide. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the ACEIs: benazepril (Lotensin and various generics), captopril (Capoten and various generics), enalapril (Vasotec and various generics), fosinopril (Monopril and various generics), lisinopril (Prinivil, Zestril, and various generics), trandolapril (Mavik), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), and ramipril (Altace), as well as their respective combinations with hydrochlorothiazide (HCTZ), if any. The ACEI class is in the top 10 of Military Health System (MHS) drug class expenditures at $75M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension. The P&T Committee recognized that there are differences in efficacy for myocardial infarction, heart failure, diabetic nephropathy and patients at high cardiovascular risk. These differences were incorporated into the cost-effectiveness analysis (CEA). The P&T Committee concluded that moexipril, perindopril, and quinapril were not cost-effective relative to the other ACEIs, since these agents were more costly and less effective. Although ramipril was shown to be more costly and more effective in the CEA, the P&T Committee did not value ramipril's clinical outcome evidence in high-risk cardiovascular patients enough to overcome its significantly higher cost (10-fold higher than the most cost-effective agent).

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the ACEIs, and other relevant factors, the P&T committee recommended (16 for, 0 against, 0 abstained, 1 absent) that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified as non-formulary under the UF, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the UF (see paragraphs 8A and 8B on pages 11 –15 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: "The Committee conducted a thorough review of the ACE inhibitor class of medications. One agent, Altace, was very carefully assessed. It provides clinical value to a small subset of beneficiaries, based on clinical trial criteria – HOPE trial. Applying medical necessity criteria, any MHS beneficiaries who meet HOPE trial criteria, will receive Altace, even following this formulary decision."

B. COMMITTEE ACTION: Based on the clinical evaluations of moexipril, perindopril, quinapril, and ramipril, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 against, 0 abstained, 2 absent) medical necessity criteria for moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any). See paragraph 8C on pages 15 – 16 of P&T Committee minutes for criteria.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving ramipril, moexipril, perindopril, or quinapril, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) an effective date no later than the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 8D on page 16 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (15 for, 0 against, 1 abstained, 1 absent) to recommend lisinopril, lisinopril/HCTZ, and captopril as the Basic Core Formulary (BCF) agents (see paragraph 8E on pages 16 – 17 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. CALCIUM CHANNEL BLOCKER (CCB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the nine CCBs marketed in the U.S.: the dihydropyridines nifedipine (Procardia, Adalat CC, and various generics), nicardipine (Cardene and Cardene SR), isradipine (DynaCirc and DynaCirc SR), felodipine (Plendil and various generics), amlodipine (Norvasc), nisoldipine (Sular), and nimodipine (Nimotop); and the non-dihydropyridines diltiazem (Cardizem, Cardizem CD, Cardizem LA, Tiazac, and various generics) and verapamil (Verelan, Verelan PM, Covera HS, Calan, Calan SR, and various generics). (See Table 3, Appendix C for a full listing of the CCBs that were

evaluated.) CCBs have extensive use in all DoD pharmacy points of service and a rank of 9th ($121M) in terms of total MHS drug expenditures.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that (1) all eight CCBs have similar relative clinical effectiveness for treating hypertension; (2) that there is insufficient evidence to conclude that any one of the following CCBs (verapamil, diltiazem, nifedipine, amlodipine, nisoldipine, nicardipine, or isradipine) is superior for reducing risk of cardiovascular outcomes in patients with hypertension, and that there is no evidence for felodipine; (3) that there is no evidence of a difference in improving symptoms of angina with amlodipine, nifedipine, diltiazem, nisoldipine, nicardipine, or verapamil, and that there is no evidence for felodipine or isradipine; (4) that amlodipine and felodipine do not adversely or positively affect mortality or morbidity in patients with systolic dysfunction; (5) that there is insufficient evidence to clearly differentiate the CCBs on the basis of adverse events, and that the overall incidence of edema ranges between 8-10%; and (6) none of the CCBs can be designated as non-formulary under the UF based solely on the clinical evidence.

The P&T concluded (17 for, 0 against, 0 abstained, 0 absent) that isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA were not cost-effective compared to nifedipine immediate release, nifedipine extended release, felodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release, and diltiazem extended release. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the CCBs, the P&T Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend formulary status for nifedipine immediate release, nifedipine extended release, felodipine, nimodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release, and diltiazem extended release, and non-formulary status for isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA. Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other CCBs, as they are not used for cardiovascular conditions (see paragraph 9A & B on pages 17 – 24 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (17 for, 0 against, 0 abstained, 0 absent) medical necessity criteria for the isradipine immediate release and isradipine controlled release, nicardipine

immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA (see paragraph 9C on page 25 of P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently using a CCB recommended for non-formulary status on the UF (268,00 patients, 73% of MHS patients receiving CCBs), the P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) an effective date no later than the first Wednesday following a 150-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9D on page 25 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing nifedipine extended release (vote: 17 for, 0 opposed, 0 abstained, 0 absent); verapamil sustained release (vote: 17 for, 0 opposed, 0 abstained, 0 absent), and diltiazem extended release (vote: 17 for, 0 opposed, 0 abstained, 0 absent) on the BCF. (See paragraph 9A and 9B on pages 17 – 24 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

10. ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERTROPHY (BPH) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the alpha blockers used to treat BPH. Four agents were considered in the review, and were classified as either selective or non-selective based upon the agent's target receptor subtype. The two non-selective agents considered in the review were doxazosin (Cardura and various generics) and terazosin (Hytrin and various generics). The two selective agents were alfuzosin (Uroxatral) and tamsulosin (Flomax). There has been an increase in the use of selective BPH alpha blockers over the past several years resulting in the entire class (selective and non-selective) being ranked 32nd in terms of annual MHS drug class expenditures at $38M.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that none of the alpha blockers have a significant clinically meaningful therapeutic

advantage in terms of efficacy over other alpha blockers; however, the selective agents may have a marginal benefit over the non-selective agents with respect to safety and tolerability. Within subgroups, the two non-selective agents (doxazosin and terazosin) were found to be similar in terms of cost-effectiveness; however, tamsulosin was found not to be cost-effective relative to alfuzosin in the selective alpha blocker sub-class. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the BPH alpha blockers, and other relevant factors, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) that tamsulosin be classified as non-formulary under the UF, and that doxazosin, terazosin, and alfuzosin be classified as formulary under the UF (see paragraphs 10A and 10B on pages 25 – 28 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of tamsulosin, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) medical necessity criteria for tamsulosin (see paragraph 10C on page 28 of P&T Committee minutes for criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving tamsulosin from one of the three MHS pharmacy points of service (89,926 patients, 46% of all patients receiving alpha blockers), the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) an effective date no later than the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 10D on pages 28 – 29 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 against, 0 abstained, 1 absent) to recommend terazosin and alfuzosin as the BCF agents (see paragraph 10E on page 29 of P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

11. ANTIDEPRESSANTS (EXCLUDING MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS)

Portions of the clinical review were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and economic analyses will be completed during the November 2005 meeting; no action necessary.

12. CHOLINESTERASE AND N-METHYL D-ASPARTATE (NMDA) INHIBITORS FOR ALZHEIMER'S DISEASE

Portions of the clinical review were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and economic analyses will be completed during the November 2005 meeting; no action necessary.

APPENDIX A – TABLE 1: Implementation Status of UF Decisions

APPENDIX B – TABLE 2: Newly Approved Drugs

APPENDIX C – TABLE 3: Calcium Channel Blockers

APPENDIX D – TABLE 4: Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

// William Winkenwerder, Jr.//
William Winkenwerder, Jr., M.D.
Date: 13 October 2005

Department of Defense
Pharmacy and Therapeutics Committee Minutes

19 August 2005

1. CONVENING

The DoD Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 17, 18, and 19 August 2005 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
MAJ Travis Watson, MS, USA	Alternate, DoD Pharmacy Programs, TMA
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Lt Col Everett McAllister, BSC	Air Force, Pharmacy Officer
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Roger Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
COL Isaiah Harper, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS, USA	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx

B. Voting Members Absent

CDR William Blanche, MSC	Director, DoD Pharmacy Programs, TMA
LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
Joe Canzolino	Department of Veterans Affairs

C. Non-Voting Members Present

Lynn T. Burleson	Assistant General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

COL Kent Maneval, MS, USA	Defense Medical Standardization Board

E. Others Present

Col Gregory Wickern, MC	Air Force, Alternate for Internal Medicine (present only 19 August)
Mr. Dan Remund	DoD Pharmacoeconomic Center (present only 17 August)
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CAPT Donald Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col Barbara Roach, MC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center (present 18 & 19 August)
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	Reservist, Assigned to DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Francine Goodman	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

Dr. William Winkenwerder, Jr., M.D. approved the minutes of the May 2005 DoD P&T Committee on 14 July 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. DoD P&T Committee Charter – CAPT Buss reported that the charter has been changed to provide for the following: Each voting member and non-voting member may have a designated alternate who can represent the member, including voting (if representing a voting member), at P&T Committee meetings in the event the member cannot attend.

5. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing: TMA briefed the members of the DoD P&T committee regarding the 27 June 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions: PEC staff and TMA briefed the members of the Committee on the implementation status of UF decisions arising from the February and May 2005 meetings (see Table 1, Appendix A). The Committee noted that the five drug classes reviewed at the February and May 2005 meetings represent 12% of total Military Health System (MHS) drug spend dollars. These five drug classes plus the four drug classes covered by existing pharmaceutical contracts represent 30% of all MHS drug spend dollars.

6. REVIEW OF RECENTLY-APPROVED AGENTS

The PEC presented clinical information on five new medications approved by the U.S. Food and Drug Administration (FDA), and introduced to the U.S. market since February 2005 (see Table 2, Appendix B). Four of the five medications fall into drug classes not yet reviewed by the DoD P&T Committee; therefore, UF consideration of these medications was deferred until drug class reviews are completed.

The fifth medication is a new sildenafil product that is FDA-approved for the treatment of pulmonary arterial hypertension (also known as primary pulmonary hypertension (PPH)) and marketed under the name of Revatio. Revatio is supplied as a 20-mg tablet, and must be given three times daily for the treatment of PPH; it is not approved for erectile dysfunction. Viagra, which is approved only for erectile dysfunction, is available in 25-, 50-, and 100-mg tablets. Viagra (sildenafil) and a similar medication, Cialis (tadalafil), are non-formulary under the UF.

Since the phosphodiesterase-5 (PDE-5) inhibitors were reviewed in May 2005, the Committee considered Revatio to be a newly-approved medication in a previously reviewed drug class. The Committee considered the following issues with regard to Revatio:

- Existing medical necessity criteria for Viagra allow reduction of the non-formulary cost share to the formulary cost share in patients with PPH.
- The clinical and cost effectiveness of Revatio relative to other medications used for the treatment of this rare, serious condition (e.g., eproprostenol, treprostinil, bosentan).

***COMMITTEE ACTION*:** The Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend that Revatio be added to the UF. The Committee decided not to recommend a change in existing prior authorization (PA) criteria for Viagra to preclude its use for PPH, since some patients may be stabilized on Viagra.

The Committee noted that PA requirements previously established for the PDE-5 inhibitor drug class apply to Revatio. A PA is required for all patients receiving sildenafil (Revatio or Viagra) for PPH.

Since all patients receiving Revatio must meet PA requirements, the Committee did not recommend a specific quantity limit for Revatio. Quantity limits for Cialis, Levitra, and Viagra for the treatment of erectile dysfunction (combined limit of 6 units per 30 days, or 18 per 90 days) continue to apply at all DoD points of service.

7. PA REQUIREMENTS FOR PRAMLINTIDE (SYMLIN) INJECTION

At the May 2005 meeting, the Committee discussed the potential need for a PA requirement for pramlintide (Symlin) subcutaneous injection, and requested that the PEC develop PA criteria to be reviewed at the next meeting. Pramlintide, which is used with insulin by diabetic patients to improve blood glucose control after meals, presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for interaction with other medications, and required adjustment of insulin dosing due to the potential for severe

hypoglycemia. Labeling for pramlintide includes specific recommendations for patient selection. Pramlintide should only be used by patients who have not reached their blood glucose goals despite managing their insulin therapy and diet well, monitoring blood glucose as directed, and following up with their providers on a regular basis. Patients using pramlintide must understand how to adjust pramlintide and insulin doses and be able to recognize hypoglycemia. Pramlintide is not indicated for use in pediatric patients.

***COMMITTEE ACTION*:** Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a PA be required for pramlintide (17 for, 0 against, 0 abstained, 0 absent). The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. In order to avoid interruptions in therapy, which would require adjustments in insulin dosage, and potentially cause disruptions in blood glucose control for patients stabilized on therapy, the Committee further recommended that patients who received pramlintide from a DoD pharmacy point of service prior to the PA effective date should be allowed to continue to receive pramlintide. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (17 for, 0 against, 0 abstained, 0 absent). PA approvals would be valid indefinitely.

Coverage is provided for the use of pramlintide as an adjunct treatment in type 1 and type 2 diabetic patients 18 or older who use mealtime insulin therapy and who meet all of the following criteria:

- are currently on insulin
- have a glycosylated hemoglobin (HbA1c) $\leq$ 9%
- are monitoring blood glucose levels frequently (at least 3 or more times per day)
- have failed to achieve adequate control of blood glucose levels despite individualized management of their insulin therapy
- are receiving ongoing care under the guidance of a health care provider skilled in use of insulin and supported by the services of a diabetic educator

Coverage is not provided for patients who:

- have poor adherence to their current insulin regimen or blood glucose monitoring
- have a HbA1c > 9%
- have experienced recurrent severe hypoglycemia requiring assistance within the past 6 months
- have experienced the presence of hypoglycemia unawareness
- have a confirmed diagnosis of gastroparesis or require the use of drugs to stimulate gastrointestinal motility

8. ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI) DRUG CLASS REVIEW

A. ACEI UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of the ten ACEIs marketed in the U.S.: benazepril (Lotensin and various generics), captopril (Capoten and various generics), enalapril (Vasotec and various generics), fosinopril (Monopril and various generics), lisinopril (Prinivil, Zestril, and various generics), trandolapril (Mavik), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), and ramipril (Altace) and their respective combinations with hydrochlorothiazide (HCTZ). Perindopril, ramipril, and trandolapril are not available in combination with HCTZ.

Information regarding the safety, effectiveness, and clinical outcome of these drugs was considered. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) *Safety and Tolerability:* The most common or serious adverse effects of the ACEIs are hypotension, dry cough, angioedema, hyperkalemia, rash, and acute renal impairment. Doses of captopril >100 mg have been associated with neutropenia and dysgeusia. Head to head trials of the ACEIs in hypertension, myocardial infarction (MI), and heart failure reported withdrawal rates due to adverse events ranging from 0-39%, but there were no significant differences between the ACEIs in any trial.

   Conclusion: The DoD P&T Committee concluded that there is no evidence that any ACEI is associated with a lower risk of serious complications than any other ACEI.

2) *Efficacy for Hypertension*: All ten ACEIs are approved by the FDA for treating hypertension. All ACEIs reduce blood pressure when titrated to effect.

   Conclusion: The Committee agreed that there is no evidence that any one ACEI is more efficacious than the others for lowering blood pressure.

3) *Efficacy in High Cardiovascular Risk patients:* The Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as death, MI, stroke, need for dialysis or renal transplantation) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in lab values).

   Three ACEIs have been evaluated in large, well-conducted randomized trials enrolling more than 8,000 high cardiovascular risk patients. In the HOPE trial, ramipril 10 mg was found to reduce the incidence of cardiovascular death, all-cause death and cardiovascular events in diabetic and non-diabetic patients with severe coronary artery disease, compared with placebo. The use of appropriate background medications such as statins, aspirin, and beta blockers was low in this study. In the EUROPA trial, perindopril 8 mg reduced the incidence of cardiovascular events (non-fatal MI, unstable angina), but did not show a benefit in reducing mortality in patients with stable coronary artery disease. The PEACE trial, where trandolapril 4 mg was evaluated in patients with stable coronary artery disease, did not show a benefit of the ACEI in reducing mortality or cardiovascular events. A large percentage of patients in the PEACE trial were receiving appropriate background therapy, and > 50% had prior coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

   Ramipril when used at doses of 5-10 mg has shown a benefit in reducing cardiovascular events but not mortality in one trial enrolling 617 patients (PART-2 trial); however, no reduction in cardiovascular events was seen when ramipril doses of 1.25 mg were evaluated (DIABHYCAR trial). Quinapril was studied in one trial of 1700 patients, but no reduction in cardiovascular events was reported (QUIET trial). A small trial (229 patients) with enalapril administered with simvastatin reported a reduction in cardiovascular events.

   In DoD, it is estimated that approximately 10% of the patients receiving ramipril meet the entry criteria established for the HOPE trial, e.g., patients with a history of cardiovascular disease (coronary artery disease, stroke, peripheral vascular disease, or diabetes), and one additional risk factor, including smoking, hypertension, hyperlipidemia, or renal insufficiency.

Conclusion: The Committee agreed that in patients with high cardiovascular risk, ramipril 10 mg is the only ACEI reported to have shown a reduction in both mortality and cardiovascular events, based on the HOPE trial. Perindopril 8 mg (EUROPA), and simvastatin have shown a reduction in major cardiovascular events, but not mortality in patients with coronary artery disease. A large trial with trandolapril did not show a reduction in major cardiovascular events, but the use of appropriate background medications was high. Quinapril has also not shown a benefit in reducing cardiovascular events.

4) *Recent MI:* Placebo-controlled trials evaluating the use of ACEIs after an MI have shown a reduction in mortality with captopril, lisinopril, ramipril, and trandolapril. Enalapril and fosinopril have shown reductions in hospitalizations for heart failure.

   Conclusion: In patients following an MI, a mortality benefit has been documented with captopril, lisinopril, ramipril, and trandolapril.

5) *Chronic Heart Failure:* A meta-analysis of 32 placebo-controlled trials enrolling over 9,000 patients reported similar point estimates for a mortality reduction with benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril. When the meta-analysis was published (1995), there was limited evidence with benazepril and perindopril, and no evidence with moexipril or trandolapril. The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for treating heart failure state that the best evidence for a mortality reduction in patients with heart failure is with captopril, enalapril, ramipril, and trandolapril, as the dosage is known for these ACEIs.

   Conclusion: In patients with chronic heart failure, the best evidence for a mortality benefit has been documented with captopril, enalapril, lisinopril, ramipril, and trandolapril.

6) *Diabetic and Non-Diabetic Renal Disease:*

   Type 1 Diabetic Nephropathy: Captopril is the only ACEI approved for diabetic nephropathy, based on one long-term trial (Collaborative trial) evaluating clinical endpoints (development of end-stage renal disease and death). Lisinopril, ramipril, perindopril, and enalapril have shown benefits in reducing proteinuria, but have not been shown to prevent progression of renal failure in type 1 diabetic patients.

   Type 2 Diabetic Nephropathy: A study of ramipril 1.25 mg in type 2 diabetics with nephropathy that evaluated both cardiovascular and renal outcomes did not show a benefit over placebo, but a reduction in albumin excretion rate was noted. A trial with benazepril 10 mg in type 2 diabetic patients did show a reduction in doubling of serum creatinine and need for dialysis; however, this benefit was seen in only 21 patients. A benefit on surrogate outcomes (reduction of microalbuminuria) has been seen with enalapril, lisinopril quinapril, and ramipril.

   Non-Diabetic Renal Disease: Captopril, enalapril, benazepril, and ramipril have been shown in one meta-analysis to reduce the risk of end-stage renal disease in non-diabetic patients with renal insufficiency.

   Conclusion: For type 1 diabetic nephropathy, captopril reduced the risk of end stage renal disease and death in poorly controlled patients. Enalapril, lisinopril, ramipril, and perindopril reduce microalbuminuria, but have not been shown to reduce the risk of end stage renal disease in type 1 diabetes mellitus (DM). For type 2 diabetic nephropathy, no ACEI has shown a benefit on clinical outcomes. Lisinopril, enalapril, quinapril, ramipril

and trandolapril appear beneficial based on various surrogate markers of renal disease, but have not been shown to impact clinical outcomes in type 2 DM. In patients with non-diabetic nephropathy, benazepril, ramipril, enalapril, captopril, and enalapril have shown a reduction in clinical outcomes.

7) *Prevention of DM:* Subgroup analysis from large trials conducted with enalapril, captopril, and ramipril has shown a delay or prevention of the development of diabetes. An ongoing trial with ramipril and rosiglitazone (DREAM trial) is underway that will prospectively evaluate whether treatment with an ACEI or thiazolidinedione will delay the development of type 2 DM.

   Conclusion: Post-hoc studies with enalapril, captopril, and ramipril have shown a delay or prevention of DM, but this has not been proven in a prospectively designed trial.

Clinical Effectiveness Conclusion: The Committee concluded that (1) all ten ACEIs have similar relative clinical effectiveness for treating hypertension; (2) ramipril has shown a reduction in mortality in patients at high cardiovascular risk; (3) captopril, enalapril, ramipril, lisinopril and trandolapril have the best evidence for reducing mortality in chronic heart failure and following MI; (4) captopril has the best evidence for improving clinical outcomes in type 1 diabetic renal disease; (5) no ACEI has shown a benefit in improving clinical outcomes in type-2 diabetic disease; (6) benazepril, ramipril, enalapril, and captopril show the best evidence for improving clinical outcomes in non-diabetic renal disease; and (7) no ACE is preferable relative to another in terms of adverse events.

Two alternative methods were used for comparing ACEIs on clinical effectiveness. When DoD utilization, therapeutic overlap and quality of evidence for various conditions were considered, ramipril, lisinopril, captopril, fosinopril, benazepril, and enalapril had higher clinical utility (overall clinical usefulness) relative to quinapril, perindopril, trandolapril, and moexipril. When using another model which only evaluated quality of evidence, the resulting ranking (from highest to lowest utility) was: ramipril, trandolapril, enalapril, perindopril, captopril, lisinopril, fosinopril, quinapril, benazepril, and moexipril. The Committee considered both evaluations when formulating their recommendation.

The Committee concluded that ramipril, captopril, lisinopril, benazepril, enalapril, trandolapril, and fosinopril have increased clinical effectiveness relative to moexipril, quinapril, and perindopril.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. ACEI UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the ACEIs in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).
To determine the relative cost effectiveness of the ACEIs, two separate economic analyses were performed: a pharmacoeconomic analysis, and a budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that ACEIs have similar safety and tolerability, and similar relative clinical effectiveness in the treatment of hypertension. However the ACEIs differ in clinical outcome evidence supporting their effectiveness in patients with high cardiovascular risk, post MI, heart failure, type 1 DM mellitus, type 2 DM mellitus, and non-diabetic nephropathy patients. In other words, the agents were shown to differ in relative clinical effectiveness.

First, a cost-minimization analysis (CMA) was performed to stratify the agents solely on cost. The results of the CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included benazepril, captopril, enalapril, and lisinopril, whereas the moderate cost cluster included fosinopril and trandolapril. Moexipril, perindopril, quinapril, and ramipril were included in the high cost cluster.

Given this conclusion, the relative cost effectiveness of the agents was determined through a cost-effectiveness analysis (CEA). In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service). The effectiveness measure used for each agent was the composite score derived from the clinical effectiveness analysis that ranked the agents based on clinical outcome evidence. The results of the CEA were: captopril was the most cost-effective agent, followed by enalapril; lisinopril and benazepril, trandolapril, and ramipril were more effective but more costly; and the other agents were less cost effective.

The results of the CMA and CEA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more ACEIs be classified as non-formulary, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of ACEIs to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of ACEIs that included benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril best achieved this goal when compared to other combination groups of ACEIs, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the ACEI cost-analysis presented by the PEC. The P&T Committee concluded that moexipril, perindopril, and quinapril were not cost-effective relative to the other ACEIs, since the agents were more costly and less effective. In pharmacoeconomic terms, these agents are considered to be "dominated." Although ramipril was shown to be more costly and more effective in the CEA, the P&T Committee did not value ramipril's clinical outcome evidence in high-risk cardiovascular patients enough to overcome its significantly higher cost (10-fold higher than the most cost-effective agent). Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ACEIs, and other relevant factors, the P&T Committee recommended that moexipril, perindopril, quinapril, and ramipril be classified as non-formulary under the UF and that benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified as non-formulary under the UF, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the UF.

C. ACEI UF Medical Necessity Criteria: Based on the clinical evaluation of the ACE inhibitors and the conditions for establishing medical necessity for a non-formulary medication provided

for in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1.) Use of the formulary ACEIs (lisinopril, enalapril, captopril, benazepril, fosinopril, and trandolapril) is contraindicated, and the use of a nonformulary ACEI (ramipril, moexipril, quinapril, or perindopril) is not contraindicated.

2). The patient has experienced or is likely to experience significant adverse effects from the formulary ACEIs, and the patient is reasonably expected to tolerate a non-formulary ACEI.

3) Use of the formulary ACEI resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary ACEI, i.e., therapeutic failure as outlined on medical necessity form.

4) The patient has previously responded to a non-formulary ACEI, and changing to a formulary ACEI would incur unacceptable risk.

5) There is no alternative pharmaceutical agent on the formulary.

The Committee noted that criteria 4 and 5 would reasonably apply only to a small subset of patients receiving ACEIs, such as patients at high cardiovascular risk similar to those included in the HOPE trial.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the ACEI medical necessity criteria.

D. ACEI UF Implementation Plan: Because a substantial number of patients (158,000, or 21% of all patients receiving ACEIs) are currently receiving ramipril, moexipril, perindopril, or quinapril, the P&T Committee recommended an effective date no later than the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend an implementation period of 120 days.

E. ACE Inhibitor Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the ACEIs recommended for inclusion on the UF to select the BCF ACEIs. It had previously been decided that at least two, but no more than three ACEIs, would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

There are currently two ACEIs on the BCF: captopril and lisinopril. From a clinical and economic standpoint, captopril and lisinopril are rational selections for the BCF. Lisinopril is the highest utilized ACEI in the entire MHS (military treatment facility (MTF), TRICARE Retail Pharmacy (TRRx) program, and TRICARE Mail Order Pharmacy (TMOP)), has a wide range of FDA indications, is generically available, and has mortality data for heart failure and following MI. Captopril has a wide range of FDA indications, has mortality data for heart failure and following MI, has outcomes evidence in type 1 diabetic renal disease, is generically available, and has a short half-life which is good for titrating patients in the immediate post-MI setting and in frail patients.

Since no BCF prices were submitted for any of the ACEIs, the DoD P&T Committee evaluated the relative cost-effectiveness for BCF selection based on the cost-effectiveness information provided for the UF formulary recommendation. Both the CMA and CEA revealed that

captopril was the most cost-effective ACEI and for this reason should be maintained on the BCF. The CEA showed that lisinopril is a very cost-effective agent, and it currently has a 68% market share at the MTFs.

Additionally, there was discussion regarding addition of an ACEI in combination with HCTZ to the BCF. There currently is no designated BCF ACEI/HCTZ combination, and it was noted that some facilities have seen a shift toward an angiotensin receptor blocker (ARB)/HCTZ combination. Addition of lisinopril in combination with HCTZ is lower in cost than other ACEIs combined with HCTZ, and may offer a convenience benefit to patients.

Conclusion: The P&T Committee concurred with the recommendation to place lisinopril, lisinopril in combination with HCTZ, and captopril on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend lisinopril, lisinopril in combination with HCTZ, and captopril as the BCF agents.

9. CALCIUM CHANNEL BLOCKER (CCB) DRUG CLASS REVIEW

A. CCB UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of the nine CCBs marketed in the U.S.: the dihydropyridines (DHPs) nifedipine (Procardia, Adalat CC, and various generics), nicardipine (Cardene and Cardene SR), isradipine (DynaCirc and DynaCirc SR), felodipine (Plendil and various generics), amlodipine (Norvasc), nisoldipine (Sular), and nimodipine (Nimotop); and the non-dihydropyridines diltiazem (Cardizem, Cardizem SR, Cardizem CD, Cardizem LA, Tiazac, and various generics) and verapamil (Verelan, Verelan PM, Covera HS, Calan, Calan SR, and various generics). (See Table 3, Appendix C for a full listing of the CCBs that were evaluated.) Information regarding the safety, effectiveness, and clinical outcomes of the CCBs when used for cardiovascular conditions was considered. (Nimodipine is used for subarachnoid hemorrhage, but not for cardiovascular conditions; thus, it will not be discussed further in the clinical review.) The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) *Efficacy for Hypertension:*

Place in Therapy: The Joint National Commission VII guidelines for treating hypertension state that CCBs are not first-line antihypertensive agents. CCBs are appropriate as add-on therapy with other antihypertensive agents, or in patients with compelling indications (coronary artery disease or DM).

Efficacy of CCB vs CCB: Head-to-head trials show that all are effective at lowering blood pressure, when titrated to effect. There are no head-to-head trials of the CCBs that assess clinical outcomes, such as mortality, stroke, MI, or development of end-stage renal disease.

Efficacy of CCB vs Other Antihypertensive Agents: Sixteen large trials assessing clinical outcomes (mortality, stroke, MI, development of end-stage renal disease) have been conducted with all the CCBs, except felodipine versus other anti-hypertensive agents, including diuretics, beta blockers, ACEIs, and ARBs. The overall quality of the evidence is poor. These 16 trials reported that the CCBs were similar, but not better than the comparator drugs in reducing all-cause mortality. There were no differences between the CCBs. A meta-analysis has not been performed due to the heterogeneity of the trials, presence of patient co-morbidities, and differing clinical endpoints. Two new trials conducted with amlodipine (ASCOT and CAMELOT) do not change the efficacy assessment. Two trials evaluating felodipine with other anti-hypertensive agents did not

have proper randomization (the STOP-2 trial), or did not evaluate felodipine as monotherapy (HOT trial).

Conclusion: The DoD P&T Committee concluded that, for lowering blood pressure, there is no evidence that any one CCB is more effective relative to another. There is insufficient evidence to conclude that any one CCB (amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil) is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension. There is no evidence for felodipine when used as a monotherapy for reducing cardiovascular outcomes in patients with hypertension.

2) *Efficacy for Chronic Stable Angina*:

Place in Therapy: The ACC/AHA guidelines for treating chronic stable angina state that improved mortality has been shown with aspirin, lipid management, and beta blockers. CCBs help with improving symptoms, and are reserved for use in patients where a beta blocker is contraindicated, where beta blocker monotherapy is not successful, or in patients with unacceptable adverse effects to beta blockers.

Efficacy of CCB vs CCB for Chronic Stable Angina: There are five head-to-head trials enrolling fewer than 300 patients that have compared a CCB vs CCB, and evaluated symptom improvement (number of angina episodes/week, exercise duration, number of doses of sublingual nitroglycerin). For these five trials, there was no difference in symptom improvement with amlodipine, immediate release diltiazem, sustained release diltiazem, nisoldipine, nicardipine, or nifedipine. There have been no studies with felodipine or isradipine.

Efficacy of CCBs vs Beta Blockers for Chronic Stable Angina: Based on thirteen head-to-head trials comparing CCBs and beta blockers, diltiazem, amlodipine, nicardipine, sustained release nifedipine, nisoldipine, and verapamil all appeared to be similarly efficacious in treating angina symptoms.

Conclusion: The Committee agreed that there is no evidence to conclude that there is any difference in efficacy of amlodipine, nifedipine, diltiazem, nisoldipine, nicardipine, or verapamil in improving angina symptoms. There is no evidence for felodipine or isradipine in head-to-head trials with other CCBs.

3) *Efficacy in Systolic Dysfunction:*

Place in Therapy: The ACC/AHA guidelines for chronic heart failure do not recommend use of a CCB. However, CCBs are used in patients with systolic dysfunction to treat an underlying co-morbidity (hypertension, angina), without adversely compromising the patient's heart failure status.

Efficacy for Systolic Dysfunction: Amlodipine and felodipine have both been shown in one trial each to have no significant effect (neither positive nor negative) on all-cause mortality, or combined fatal and non-fatal events in patients with heart failure. In the V-HeFT III trial, there was no difference between placebo and felodipine in all-cause mortality in 450 patients with primarily New York Heart Association (NYHA) Class II heart failure symptoms. In the PRAISE trial, there was a 9% reduction in the relative risk of the composite outcome of all-cause mortality and cardiovascular morbidity with amlodipine, which was not significantly different from placebo, in 1,153 patients with primarily NYHA class III heart failure.

Conclusion: Based on the clinical evidence, the Committee agreed that when used in patients with heart failure, amlodipine or felodipine do not adversely affect outcomes.

4) *Safety and Tolerability:* In general, the safety profile of an individual CCB reflects its pharmacologic class. The DHPs are peripheral vasodilators, and commonly cause edema, headache, flushing, reflux tachycardia, and dizziness (especially short-acting nifedipine). Verapamil has negative inotropic effects, while diltiazem does not exhibit negative inotropy.

   There are no head–to-head trials of CCB vs CCB that assess clinical outcomes and adverse events. Individual trials in hypertension comparing the CCBs vs other anti-hypertensive agents that evaluated cardiovascular outcomes were insufficient to determine differences in the incidence of withdrawals due to adverse effects for amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine. For the trials evaluating CCBs in angina, there were no differences in withdrawal rates or adverse events with amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine. Two long-term observational studies reported that severe adverse events were highest with diltiazem, followed by verapamil, amlodipine, nifedipine, and nicardipine. Although there may be individual patient differences in the incidence of edema, the overall incidence of edema for all the CCBs ranges between 8-10%, and the rates of withdrawal due to edema are similar between CCBs.

   Conclusion: The DoD P&T Committee agreed that there is insufficient evidence to clearly differentiate the CCBs on the basis of adverse events. The most common adverse events are dizziness, peripheral edema, headache, and flushing.

5) *Other Factors:*

   Special Populations: Amlodipine is the only DHP CCB indicated for pediatric use in patients aged 6-16 years with hypertension. Diltiazem and verapamil are used in the pediatric population.

   Dosing Intervals: An evaluation of DHP dosing intervals in DoD showed that 10% of patients receiving sustained release nifedipine required more than 1 dose daily, vs 7% of amlodipine patients.

   Formulations: The CCBs are available in a variety of immediate, sustained, and extended release preparations. Generic preparations are available for several of the products, but the products may not be bioequivalent due to differing release mechanisms. However, the products can be considered therapeutically equivalent, if they contain the same active ingredient. Immediate release nifedipine is no longer used for cardiovascular conditions due to a high incidence of reflux tachycardia and associated increased mortality. There are only 2,100 unique utilizers of immediate release nifedipine (for conditions other than cardiovascular disease) in DoD. This product will not be discussed further in the clinical review.

   Chronotherapeutics: A higher incidence of cardiovascular events (stroke, MI) has been noted in the early morning hours (between 6 AM and 10 AM). The concept of chronotherapeutics theorizes that administering an anti-hypertensive agent in the evening will result in a lowered incidence of next morning cardiovascular events. The verapamil products, Verelan PM and Covera HS, and the diltiazem product, Cardizem LA, are specifically labeled for administration at bedtime. While intriguing, the concept of chronotherapeutics has not been prospectively shown to improve outcomes.

Conclusion: The Committee agreed that there are differences amongst the CCBs in terms of other factors as discussed above.

Clinical Effectiveness Conclusion: The Committee concluded that (1) all eight CCBs have similar relative clinical effectiveness for treating hypertension; (2) there is insufficient evidence to conclude that verapamil, diltiazem, nifedipine, amlodipine, nisoldipine, nicardipine, or isradipine is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension, and that there is no evidence for felodipine; (3) there is no evidence of a difference in improving symptoms of angina with amlodipine, nifedipine, diltiazem, nisoldipine, nicardipine, or verapamil, and that there is no evidence for felodipine or isradipine; (4) amlodipine and felodipine do not adversely or positively affect mortality or morbidity in patients with systolic dysfunction; (5) there is insufficient evidence to clearly differentiate the CCBs on the basis of adverse events, and that the overall incidence of edema ranges between 8-10%, and (6) none of the CCBs should be designated as non-formulary on the UF based solely on the clinical evidence.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions as stated above.

B. CCB UF Relative Cost Effectiveness:

1) DHP CCBs

a) DHP CCB UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of DHP CCBs in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but, was not limited to, sources of information listed in 32 CFR 199.21(e)(2). From the preceding relative clinical effectiveness evaluation, the P&T Committee considered the clinical merits of the DHP CCBs with regard to:

- Clinical effectiveness in the treatment of hypertension and angina
- Clinical evidence for relative safety and tolerability
- Clinical outcome evidence supporting their effectiveness in heart failure
- Place in therapy (i.e., when do national guidelines recommend the use of these agents)

To determine the relative cost-effectiveness of the agents within the DHP calcium channel blocker therapeutic class, two separate economic analyses were performed: a CMA, and a BIA.

The cost used in the CMA was the total weighted average cost per day of treatment (for all three points of service). The results of the CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included nifedipine immediate release, nifedipine extended release, and felodipine, whereas the moderate cost cluster included amlodipine, nicardipine immediate release, and nisoldipine. Isradipine immediate release, isradipine controlled release, and nicardipine sustained release were included in the high cost cluster. Based on this use of cost-minimization to determine the relative cost-effectiveness of the agents within DHP calcium channel blocker therapeutic class, nifedipine immediate release, nifedipine extended release, and felodipine were the most cost-effective agents.

The results of the CMA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that the status of one or more DHP CCBs be classified as non-formulary under the UF, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of DHP CCBs to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of DHP CCBs that included nifedipine immediate release, nifedipine extended release, felodipine, and nisoldipine best achieved this goal, when compared to other combination groups of DHP CCBs, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the DHP CCB cost-analysis presented by the PEC. The analysis concluded that isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, and amlodipine were not cost-effective relative to the other DHP CCBs. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCBs, and other relevant factors, the P&T Committee recommended that isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, and amlodipine be classified as non-formulary under the UF, with nifedipine immediate release, nifedipine extended release, felodpine, nimodipine, and nisoldipine classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that that isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, and amlodipine be classified as non-formulary under the UF, with nifedipine immediate release, nifedipine extended release, felodpine, nimodipine and nisoldipine classified as formulary on the UF. Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other CCBs, as they are not used for cardiovascular conditions.

b) DHP CCBs BCF Review and Recommendations: The P&T Committee reviewed the DHP CCBs recommended for inclusion on the UF to select the BCF DHP CCBs. It had previously been decided that one DHP calcium channel blocker could be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Currently the only DHP calcium channel blocker on the BCF is nifedipine extended release (Adalat CC or equivalent). From a clinical and cost-effective standpoint, this remains a rational selection for the BCF. MTFs continue to enjoy a good price for this agent, and the VA is expected to complete a sole-source generic contract for a nifedipine extended release product in the next few months. BCF prices were submitted for amlodipine and nisoldipine. However, the BIA revealed that neither was competitive, and that nifedipine CC was the most cost-effective DHP calcium channel blocker, and for this reason should be maintained on the BCF. MTFs can add additional DHP CCBs from the UF to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place nifedipine extended release on the BCF. As the CC formulation is currently the most cost-effective choice, the BCF listing will state that MTFs are required to carry the CC formulation of nifedipine extended release, until a new DoD/VA sole source contract for nifedipine extended release is completed.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend nifedipine extended release as the BCF agent.

2) Verapamil

a) Verapamil UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of verapamil agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). To determine the relative cost-effectiveness of the verapamil agents, two separate economic analyses were performed: a pharmacoeconomic analysis and a BIA. From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that verapamil agents have similar relative clinical effectiveness in the treatment of hypertension and angina, have similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes. Therefore, a CMA was performed to stratify the agents solely on cost. The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service).

The results of the CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included verapamil immediate release and verapamil sustained release, whereas the moderate cost cluster included the Verelan brand of verapamil extended release capsules. Verelan PM and Covera HS, two long-acting, night-time dosed verapamil brands, represented the high cost cluster. Within the verapamil CCB therapeutic subclass, verapamil immediate release and verapamil sustained release were the most cost-effective agents. The results of the CMA and CEA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that the status of one or more verapamil CCBs be changed from formulary to non-formulary such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of verapamil agents to be included on the UF, which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of verapamil agents that included verapamil immediate release and verapamil sustained release best achieved this goal when compared to other combination groups of verapamil agents, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the verapamil CCB cost-analysis presented by the PEC. The P&T Committee concluded that Verelan, Verelan PM, and Covera HS were not cost-effective relative to the other verapamil agents, as they were more costly and provided no additional clinically meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions

from the relative clinical effectiveness and relative cost effectiveness determinations of the verapamil agents, and other relevant factors, the P&T Committee recommended that Verelan, Verelan PM and Covera HS be classified as non-formulary under the UF, and verapamil immediate release and verapamil sustained release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend formulary status for verapamil immediate release and verapamil sustained release, and non-formulary status for Verelan, Verelan PM and Covera HS on the UF.

b) Verapamil BCF Review and Recommendations: The P&T Committee reviewed the verapamil agents recommended for inclusion on the UF to select the BCF verapamil agent. It had previously been decided that one verapamil agent would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Verapamil sustained release is currently on the BCF. From a clinical and economic standpoint, this remains a rational selection for the BCF. MTFs continue to enjoy a good price for this agent, which represents the majority of verapamil use in the MHS. Verapamil sustained release is currently the most cost-effective long acting verapamil agent. For this reason, it should be maintained on the BCF. MTFs may add verapamil immediate release to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concluded that verapamil sustained release should remain on the BCF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining verapamil sustained release as the BCF agent.

3) Diltiazem

a) Diltiazem UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of diltiazem agents in relation to safety, tolerability, effectiveness, and clinical outcomes to the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). To determine the relative cost-effectiveness of diltiazem agents, two separate economic analyses were performed: a pharmacoeconomic analysis and a BIA. From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that diltiazem agents have similar relative clinical effectiveness in the treatment of hypertension and angina, and similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes. Therefore, a CMA was performed to stratify the agents solely on cost. The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service).

The results of the CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included diltiazem immediate release, whereas the moderate cost cluster included diltiazem extended release and diltiazem sustained release. Cardizem LA represented the high cost cluster. The CMA

showed that diltiazem immediate release, diltiazem extended release, and diltiazem sustained release were the most cost-effective agents. The results of the CMA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with non-formulary decisions, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of diltiazem agents to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA showed that the most cost-effective combination of diltiazem agents was diltiazem immediate release, diltiazem extended release, and diltiazem sustained releae.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the diltiazem cost-analysis presented by the PEC. The analysis concluded that Cardizem LA was not cost-effective relative to the other diltiazem agents, since it was more costly and provided no additional clinically-meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the diltiazem agents, and other relevant factors, the P&T Committee recommended that Cardizem LA be classified as non-formulary under the UF Formulary, and diltiazem immediate release, diltiazem sustained release, and diltiazem extended release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend formulary status for diltiazem immediate release, diltiazem sustained release, and diltiazem extended release, and non-formulary status for Cardizem LA under the UF.

b) Diltiazem BCF Review and Recommendations: The P&T Committee reviewed the diltiazem agents recommended for inclusion on the UF to select the BCF diltiazem agent. It had previously been decided that one diltiazem agent would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Diltiazem extended release is currently on the BCF. From a clinical and economic standpoint, this remains a rational selection for the BCF. The MTFs continue to enjoy a good price for this agent, and 97% of usage in the DoD MHS is for the diltiazem extended release product. The Tiazac brand of diltiazem extended release is currently the most cost-effective diltiazem extended release agent and should be selected for the BCF. MTFs may add additional diltiazem agents from the UF to their local formularies, if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place diltiazem extended release on the BCF. As the Tiazac formulation is currently the most cost-effective choice, the BCF listing will state that MTFs are required to carry the Tiazac formulation of extended release diltiazem.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend diltiazem extended release as the BCF agent.

C. CCB UF Medical Necessity Criteria: Based on the clinical evaluation of the CCBs and the conditions for establishing medical necessity for a non-formulary medication provided for in

the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of the formulary CCBs (nifedipine immediate release, nifedipine extended release, felodipine, nimodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release and diltiazem extended release is contraindicated, and the use of non-formulary CCBs (isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA) is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary CCBs, and the patient is reasonably expected to tolerate a non-formulary CCB.

3) Use of the formulary CCBs resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary CCB [therapeutic failure as outlined on medical necessity form].

4) The patient has previously responded to a non-formulary CCB, and changing to a formulary CCB would incur unacceptable risk.

5) There is no alternative pharmaceutical agent on the formulary.

The Committee noted that criteria 4 and 5 would reasonably apply only to a small subset of patients receiving CCBs, such as patients with NYHA Class III or IV heart failure similar to those in the V-HeFT and PRAISE trials or clinically fragile patients with angina and multiple comorbidities who are stable on amlodipine. The Committee also noted that amlodipine is the only long-acting DHP CCB approved by the FDA for pediatric patients. The Committee recommended that medical necessity be automatically approved for patients younger than 18 years of age, if this is technically feasible (i.e., if the Pharmacy Data Transaction Service can be programmed to permit scripts for beneficiaries age <18 years to be filled without medical necessity being established).

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to approve the medical necessity criteria.

D. CCB UF Implementation Plan: Because a substantial number of patients (268,000, or 73% of all patients receiving CCBs) are currently receiving CCBs recommended for non-formulary status, the P&T Committee recommended an effective date no later than the first Wednesday following a 150-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend an implementation period of 150 days.

10. ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERTROPHY (BPH) DRUG CLASS REVIEW

A. Alpha Blocker UF Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of alpha blockers FDA-approved for BPH: terazosin (Hytrin and various generics), doxazosin (Cardura and various generics), alfuzosin (Uroxatral) and tamsulosin (Flomax). First-generation (phenoxybenzamine) alpha-adrenergic antagonists have been replaced by second generation (terazosin, doxazosin) and third-generation (tamsulosin, alfuzosin) alpha blockers. The clinical review included consideration of pertinent information

from a variety of sources determined by the P&T Committee to be relevant and reliable, including, but not limited to, sources of information listed in 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The P&T Committee agreed that in the MHS, alpha blockers are considered a gold standard for treating symptoms of BPH. During a twelve-month period ending 30 April 2005, approximately 196,388 patients were prescribed an alpha blocker. This class is now ranked 25th in MHS drug class expenditures.

Efficacy: All alpha blockers are FDA-approved for the treatment of BPH. There are limited head-to-head trials comparing the four alpha blockers. The available placebo controlled trials, and meta-analyses were reviewed. Although all alpha blockers were found to be clinically effective when compared to placebo, variability in study design, demographics, and outcome measures precluded the ability to designate one alpha blocker as clinically superior. The Cochrane Database, Clinical Evidence, and the American Urological Association (evidence-based healthcare systematic reviews) concurred that all four alpha blockers are clinically interchangeable in regards to efficacy. In the tools used to measure effectiveness, all four drugs relieve BPH symptoms, improve standardized testing symptom scores, and improve urinary flow rates to the same extent. The alpha blockers appear to be similar in terms of clinical efficacy.

Safety/Tolerability: The P&T Committee found that the alpha blockers had similar safety data within their generation with respect to drug interactions, and adverse drug reactions. Adverse effects are primarily related to the agent's target receptor subtype (terazosin and doxazosin are nonselective; alfuzosin and tamsulosin are selective). As of August 2005, all agents have similar alpha-blocker postural hypotension warnings. Nonselective alpha blockers exhibit a higher rate of vasodilatory adverse effects (dizziness, asthenia, postural hypotension) relative to selective alpha blockers. Alfuzosin and tamsulosin appear to be better tolerated than terazosin and doxazosin as measured by withdrawals due to adverse events and discontinuation of therapy.

Conclusion: The P&T Committee concluded that there is no compelling evidence to support clear superiority of one agent over another in terms of efficacy. All alpha blockers have been shown to have a positive effect on the symptoms of BPH. Selective alpha blockers appear to have a lower rate of adverse vasodilatory effects, a safety/tolerability advantage.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) that for the purposes of the UF clinical review, all alpha blockers have similar efficacy for treating BPH. All alpha blockers have similar safety and tolerability profiles within alpha blocker generations.

B. Alpha Blocker Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the agents within the alpha blocker class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

To determine the relative cost-effectiveness of the agents within the alpha blocker therapeutic class, two separate economic analyses were performed, a pharmacoeconomic analysis and a BIA. From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that alpha blockers have similar relative clinical effectiveness in the treatment of lower urinary tract symptoms often associated with BPH, but differ in safety and tolerability, especially in comparison to non-selective alpha blockers with selective alpha blockers. The agents within the alpha blocker therapeutic class were thus shown to differ in relative clinical effectiveness.

First, a CMA was performed to stratify the agents on cost. The results of the CMA revealed that non-selective alpha blockers were more cost-effective compared to non-selective alpha blockers, by nearly ten-fold based on the total weighted average cost per day of treatment (for all three points of service). Within the non-selective alpha blocker sub-class, doxazosin was found to be slightly more cost-effective compared to terazosin and within the selective alpha blocker sub-class alfuzosin was found to be considerably more cost-effective compared to tamsulosin (alfuzosin cost per day of treatment was 20% lower than tamsulosin's cost per day of treatment).

Given this conclusion, a CEA was employed, which accounted for differences in safety and tolerability between the non-selective alpha blocker sub-class and the selective alpha blocker sub-class. In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). For this particular CEA, a Markov model was constructed based upon the outcomes reported in the Medical Therapy of Prostatic Symptoms Study (MTOPS) for the doxazosin arm. The drug cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service). Direct medical costs associated with disease clinical progression and treatment of adverse drug events were also incorporated into the model.

Two CEAs were performed. In the first analysis, the effect (outcome) was defined as successfully treated patients. In the second analysis, the effect was defined as successfully treated patients without adverse drug events, more specifically, cardiovascular/ hypotensive adverse drug events associated with non-selective alpha blockers. The overall results from the first CEA paralleled the results obtained in the CMA: non-selective alpha blockers and selective alpha blockers were equally effective, non-selective alpha blockers were more cost-effective compared to selective alpha blockers, doxazosin was slightly more cost-effective compared to terazosin, and alfuzosin was considerably more cost-effective compared to tamsulosin. However, when the cost of adverse events associated with non-selective alpha blocker treatment was considered, the difference in cost per successfully treated patient between the non-selective and selective alpha blockers was two-fold, not ten-fold (as shown in the CMA). The results from the second CEA revealed selective alpha blockers were more effective (more patients successfully treated without adverse drug events), but more costly compared to non-selective alpha blockers. Although there was still approximately a two-fold difference in cost of treatment between the non-selective and selective alpha blockers, the incremental cost was less compared to the first CEA.

The results of the CMA and CEA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more alpha blockers be classified as non-formulary, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of alpha blockers to be included on the UF which best met the

majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of alpha blockers that included alfuzosin, doxazosin, and terazosin best achieved this goal when compared to other combination groups of alpha blockers, and thus were determined to be more cost-effective relative to other combination groups.

*Conclusion**:*** The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the BPH alpha-blocker cost-analysis presented by the PEC. The P&T Committee concluded that doxazosin and terazosin had similar relative cost-effectiveness in the non-selective alpha blocker subclass, but determined that tamsulosin was not cost-effective relative to alfuzosin in the selective alpha blocker sub-class. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee recommended that tamsulosin be classified as non-formulary under the UF, and that doxazosin, terazosin, and alfuzosin be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend formulary status for doxazosin, terazosin, and alfuzosin, and non-formulary status for tamsulosin under the UF.

C. Alpha Blocker UF Medical Necessity Criteria: Based on the clinical evaluation of the alpha blockers and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of a formulary alpha blocker (terazosin, doxazosin, alfuzosin) is contraindicated, and the use of a nonformulary alpha blocker (tamsulosin) is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from a formulary alpha blocker, and the patient is reasonably expected to tolerate a non-formulary alpha blocker.

3) Use of the formulary alpha blocker resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary alpha blocker [therapeutic failure as outlined on medical necessity form].

Because the UF would include both selective and nonselective agents, the Committee agreed that the situations covered by general criterion 4 (changing to a formulary agent would incur unacceptable risk) and general criterion 5 (no alternative pharmaceutical agent on the formulary) would not apply in this category. The Committee also noted it would be reasonable for a patient who experienced adverse effects (e.g., dizziness, postural hypotension) on terazosin or doxazosin, and who could not be treated with alfuzosin, to meet medical necessity requirements for tamsulosin without requiring that the patient fail or be unable to take both formulary non-selective agents.

D. Alpha Blocker UF Implementation Plan: Because a number of patients are currently receiving tamsulosin from one of the three MHS pharmacy points of service (89,926 patients, 46% of all patients receiving alpha blockers), the P&T Committee proposed a 120-day transition period for implementation of the decision to classify tamsulosin as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) an effective date no later than the first Wednesday following a 120-day

implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Alpha-Blocker Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the alpha blockers recommended for inclusion on the UF to select the BCF alpha blockers. It had previously been decided that at least one, but no more than two alpha blockers, would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Terazosin is currently the only alpha blocker on the BCF, has a current MTF market share of 63%, and, when properly titrated, is safe and effective in the majority of patients requiring treatment for BPH. Although marginally less costly, doxazosin has a much lower MTF market share and offers no clinical advantage compared to terazosin.

There are three arguments supporting placement of alfuzosin on the BCF:

1) Provides increased access to a selective alpha blocker for MTF patients who cannot tolerate a non-selective alpha blocker, or in whom a non-selective alpha blocker is contraindicated due to co-morbid conditions
2) The CEA suggests the difference in the cost of treatment between selective alpha blocker and non-selective alpha blocker is not ten-fold (total weighed average cost per day of treatment at all three points of service), but closer to two-fold when the costs of non-selective alpha blocker adverse drug events are considered.
3) Based on the total weighted average cost per day of treatment for MTFs, alfuzosin is 43% less costly than tamsulosin.

The primary disadvantage of adding a selective alpha blocker to the BCF is that it would require those MTFs who currently do not have a selective alpha blocker on their formulary to add alfuzosin, and thus increase MTF pharmacy expenditures. However, utilization of selective alpha blockers is increasing at MTFs, and adding alfuzosin now would reduce the unit cost for a selective alpha blocker.

Conclusion: The P&T Committee recommended placing alfuzosin and terazosin on the BCF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend alfuzosin and terazosin as the BCF agents.

11. ANTIDEPRESSANTS (EXCLUDING MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS)

PEC staff presented a clinical review of the antidepressant medications listed below to the Committee. Although the receptor-binding characteristics and pharmacological classification of these medications vary, the Committee agreed that there is sufficient overlap in their clinical use to review them as a single class of medications.

- *Selective Serotonin Reuptake Inhibitors (SSRIs)* - citalopram, escitalopram (Lexapro), fluoxetine, fluvoxamine, paroxetine, and sertraline (Zoloft)
- *Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)* - venlafaxine (Effexor, Effexor XR), duloxetine (Cymbalta)
- *Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)* - bupropion
- *Alpha-2 antagonists* - mirtazapine
- *Serotonin modulators* – nefazodone, trazodone

Seven of these medications are currently on the BCF: the SSRIs citalopram, fluoxetine (excludes Sarafem, Prozac Weekly), paroxetine (excludes Paxil CR), and sertraline; the SNRI venlafaxine sustained release (Effexor XR); the NDRI bupropion sustained release (excludes Wellbutrin XL); and the serotonin modulator trazodone.

The Committee provided expert opinion regarding the key questions in this drug class and clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Both the clinical and cost effectiveness analyses will be completed during the November 2005 meeting; no action necessary.

12. CHOLINESTERASE AND N-METHYL D-ASPARTATE (NMDA) INHIBITORS FOR ALZHEIMER'S DISEASE

PEC staff presented a clinical review of the cholinesterase and NMDA inhibitors used for the treatment of Alzheimer's disease. The agents in this class include: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne, formerly Reminyl), and memantine (Namenda). The current BCF agent for this class is donepezil.

The Committee provided expert opinion regarding the key questions in this drug class and clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and cost-effectiveness analyses will be completed during the November 2005 meeting; no action necessary.

13. ADJOURNMENT

The third day of the meeting adjourned at 1230 hours on August 18, 2005. The dates of the next meeting are November 16–18, 2005.

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Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1: Implementation Status of UF Decisions

Appendix B – Table 2: Newly Approved Drugs

Appendix C – Table 3: Calcium Channel Blockers

Appendix D – Table 4: Abbreviations

Appendix A – Table 1: Implementation Status of UF Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Non-Formulary Decision**	**BCF/ECF**
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05: MTFs may add vardenafil to formulary based on local needs
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05: MTFs must have nystatin and clotrimazole topical products on formulary.
May 05	MS-DMDs	-	ECF	Interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05: MTFs must have Avonex on formulary if local needs necessitate having medications in this class on formulary.
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05: MTFs must have telmisartan and telmisartan/HCTZ on formulary.
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05: MTFs must have omeprazole and rabeprazole on formulary.

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; MN = Medical Necessity; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; ARBs = Angiotensin Receptor Blockers; PPIs = Proton Pump Inhibitors; HCTZ = hydrochlorothiazide

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2: Newly Approved Drugs

Medication & Mechanism of Action	FDA Approval Date; FDA-Approved Indications	Committee Recommendation
Sildenafil (Revatio; Pfizer)	6 Jun 2005; treatment of pulmonary arterial hypertension (WHO group I) to improve exercise capacity. Efficacy has not been evaluated in patients currently on bosentan therapy. Pulmonary arterial hypertension is also known as primary pulmonary hypertension.	UF Drug Class: PDE-5 Inhibitors Committee Recommendation: Add to the UF Note: Prior authorization (PA) requirements previously established for the PDE-5 inhibitor class apply to Revatio. Since all patients receiving Revatio must meet PA requirements, the Committee did not recommend a specific quantity limit.
Exenatide injection (Byetta; Amylin)	28 Apr 2005; adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Isosorbide dinitrate / hydralazine tabs (BiDil; Nitromed)	23 Jun 2005; treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Bromfenac ophthalmic solution 0.09% (Xibrom; ISTA)	24 Mar 2005; indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Paracalcitol caps (Zemplar; Abbott) Synthetically manufactured analog of calcitriol, the metabolically active form of Vitamin D	26 May 2005; prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 3 and 4. [The injectable formulation is approved for patients requiring dialysis (stage 5).]	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – Table 3: Calcium Channel Blocker Brand and Generic Names

Generic Name	Brand (Manufacturer)	Generic products available
Dihydropyridines (DHPs)		
Amlodipine	***Norvasc*** (Pfizer)	**No**
Felodipine	Plendil (AstraZeneca)	Yes
Isradipine	***DynaCirc*** [immediate release formulation] (Reliant)	**No**
	DynaCirc CR (Reliant) [Gastrointestinal Therapeutic System (GITS)]	**No**
Nicardipine	Cardene [immediate release formulation] (Roche)	Yes
	Cardene SR (Roche) [granules/powder mix]	**No**
Nifedipine	**Immediate Release***	
	Procardia (Pfizer)	Yes
	Extended Release	
	Adalat CC (Bayer); Afeditab CR (Watson); Nifediac CC (Teva); [core coat]	Yes
	Procardia XL (Pfizer); Nifedical XL (Teva) [GITS]	Yes
Nimodipine	Nimotop*	No
Nisoldipine	***Sular*** (First Horizon) [core coat]	**No**
Non-dihydropyridines (non-DHPs): Verapamil products		
Verapamil	**Immediate Release**	
	Isoptin (FSC); Calan (Searle)	Yes, to Isoptin
	Sustained Release	
	Calan SR; Isoptin SR (Par)	Yes to Isoptin SR
	Extended Release	
	Verelan (Elan)	**No**
	Extended Release for bedtime dosing	
	Verelan PM (Elan)	**No**
	Covera HS (Searle)	**No**
Non-dihydropyridines (non-DHPs): Diltiazem products		
Diltiazem	**Immediate Release**	
	Cardizem (Kos)	Yes
	Sustained Release	
	Diltiazem HCL (Cardizem SR)	Yes
	Extended Release	
	Cardizem CD (Biovail)	Yes, except 360 mg does not have generics
	Dilacor XR (Watson); Diltia XT (Andrx)	Yes
	Cardizem CD; Cartia XT (Andrx)	Yes
	Tiazac (Biovail), Taztia XT (Andrx)	Yes
	Tiazac (Forest, Inwood)	Yes, except 420 mg does not have generics
	Extended Release for bedtime dosing	
	Cardizem LA (Kos)	**No**

***Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other calcium channel blockers, as they are not used for cardiovascular conditions.**

Appendix D – Table 4: Table of Abbreviations

ACC	American College of Cardiology
ACEI	angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPH	benign prostatic hypertrophy
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost-minimization analysis
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
FDA	Food and Drug Administration
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HCTZ	hydrochlorothiazide
MHS	Military Health System
MI	myocardial infarction
MTF	military treatment facility
NDRI	norepinephrine dopamine reuptake inhibitor
NYHA	New York Heart Association
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE-5	phosphodiesterase-5
PEC	Pharmacoeconomic Center
PPH	primary pulmonary hypertension
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy
UF	Uniform Formulary
VA	Veterans Administration

19 May 2005

DECISION PAPER:

MAY 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

5. ITEMS FOR INFORMATION

6. REVIEW OF RECENTLY APPROVED AGENTS

7. BASIC CORE FORMULARY (BCF) CLARIFICATION OF RECENTLY APPROVED DRUGS

The DoD Pharmacy and Therapeutics (P&T) Committee reviewed the relative clinical and cost effectiveness of the following recently approved formulations of medications already listed on the BCF.

A. Alendronate 70 mg / cholecalciferol (vitamin D) 2800 IU (Fosamax Plus D)

The current BCF listing for alendronate includes all oral strengths except for 40 mg tablets, which are indicated only for the treatment of Paget's disease. Currently, the majority of use across DoD is of the weekly formulations of alendronate (35- and 70-mg tablets). Addition of vitamin D, which is required for normal bone formation, to alendronate may provide a clinical advantage for patients who have inadequate dietary intake of vitamin D and insufficient exposure to sunlight. Taking into account the manufacturer's offer to add alendronate plus D to the current BPA for alendronate without an increase in price, and because the product is not expected to delay the availability of generic versions of alendronate or alendronate plus vitamin D, the Committee agreed that the product offers a small clinical advantage to military treatment facility (MTF) patients at no additional cost. (See paragraph 7 A. on page 13 of P&T Committee minutes.)

COMMITTEE ACTION: The Committee recommended adding alendronate plus D to the BCF (17 for, 1 abstained, 1 absent).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. Fluticasone Propionate HFA (Flovent HCA)

The current BCF listing is for fluticasone oral inhaler. The manufacturer is no longer manufacturing the chlorofluorocarbon (CFC)-containing product (Flovent) and is replacing it with a hydrofluoroalkane (HFA)-containing product (Flovent HFA). Since the product is now the only fluticasone metered dose inhaler available and since the HFA product does not appear to offer any clinical disadvantages compared to the CFC product, the Committee agreed that there was no need to clarify the current BCF listing. As of May 2005, the Flovent HFA metered dose inhaler was available to MTFs and the mail order program at the same price as the old CFC formulation. (See paragraph 7 B. on pages 13-14 of P&T Committee minutes.) No action taken.

C. Insulin Glargine (Lantus) 100 u/mL 3 mL cartridges

The current BCF listing is for insulin glargine injection (Lantus), which was previously available only as a 10 mL vial. The 3 mL cartridges are designed for use with the manufacturer's OptiClik device. The Committee agreed that while this device may benefit some patients (e.g., patients who are needle-phobic or visually impaired), the number of patients who would benefit represents only a small percentage of patients using insulin glargine. The Committee noted that, overall, about 92% of insulin use in DoD is vials, with insulin pens, cartridges, and dispensing syringes representing only 8% of use. The Federal Supply Schedule (FSS) price (as of May 2005) for Lantus was $25.70 for the 10 mL vial ($2.67 per mL) vs. $79.09 for a box of five 3 mL cartridges ($5.27 per mL). The Committee agreed that the potential clinical benefit associated with use of the cartridges was not sufficient to justify the additional cost. (See paragraph 7 C. on page 14 of P&T Committee minutes.)

COMMITTEE ACTION: The Committee recommended clarifying the current BCF listing for insulin glargine injection to exclude the 100 u/mL 3 mL cartridges (18 for, 1 abstained).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

8. PHOSPHODIESTERASE-5 (PDE-5) INHIBITOR DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the three PDE-5 inhibitors: sildenafil (Viagra), vardenafil (Levitra); and tadalafil (Cialis). There has been an increase in the use of PDE-5s over the past five years, placing this class in the top 50 of Military Health System (MHS) drug class expenditures.

A. COMMITTEE ACTION: The P&T Committee concluded that none of the PDE-5 inhibitors have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other PDE-5 inhibitors. (See paragraph 8 A. on pages 14-15 of P&T Committee minutes.) The Committee concluded that sildenafil and

tadalafil were not cost effective relative to vardenafil. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PDE-5 inhibitors, the P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend formulary status for vardenafil and non-formulary status for sildenafil and tadalafil under the Uniform Formulary (UF). (See paragraph 8 B. on pages 15-16 of P&T Committee minutes) Under 32 C.F.R. 199.21(g)(3), no pharmaceutical agent may be designated as non-formulary on the UF unless preceded by such recommendation by the P&T Committee.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of sildenafil and tadalafil, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended medical necessity criteria for the sildenafil and tadalafil (18 for, 0 opposed, 0 abstained). (See paragraph 8 C. on page 16 of P&T Committee minutes for criteria)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving either sildenafil or tadalafil (128,007 patients, 90% of all patients receiving PDE-5 inhibitors), the P&T Committee recommended (17 for, 1 opposed, 1 abstained) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8 D. on pages 16-17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing vardenafil on the Extended Core Formulary (ECF) (17 for, 0 opposed, 1 abstained, 1 absent). Because there are no other formulary PDE-5 inhibitors on the UF, MTFs are prohibited from adding additional PDE-5 inhibitor(s) to their local formularies. (See paragraph 8 E. on page 17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR DRUG CLASS REVIEW

Portions of the clinical review were presented to the P&T Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Two ACE inhibitors, available as multisource generics for approximately two years, recently suspended manufacturing secondary to litigation results. The Committee will seek pricing information from the companies representing the name brand version of these products. Both the clinical and cost effectiveness analyses will be completed during the August 2005 meeting; no action necessary.

10. MULTIPLE SCLEROSIS DISEASE MODIFYING DRUG (MS-DMD) CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the four MS-DMDs: intramuscular interferon (IFN) beta-1a (Avonex), subcutaneous IFN beta-1a (Rebif), subcutaneous IFN beta-1b (Betaseron), and the subcutaneous polypeptide mixture glatiramer acetate (Copaxone). MS-DMDs have been available for the past 12 years and the class is currently ranked 33rd in MHS drug class expenditures. During a twelve-month period ending 31 January 2005, approximately 6,500 patients were prescribed a MS-DMD. In most cases MS-DMDs are prescribed by sub-specialists (neurologists).

A. COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to accept the conclusion that none of the MS-DMDs have a significant clinically meaningful therapeutic advantage in terms of safety, tolerability and effectiveness over the other MS-DMDs. (See paragraph 10 A. on pages 17-18 of P&T Committee minutes for rationale.) The P&T Committee also concluded that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex. (See paragraph 10 B. on page 18 of P&T Committee minutes for rationale.) Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MS-DMDs, and other relevant factors (i.e., relative uniqueness of each agent in patient therapy and the low expectation that patient behavior would be affected by formulary status), the P&T Committee voted (18 for, 0 opposed, 0 abstained) to recommend formulary status for all four MS-DMDs:

IFN beta-1a (Avonex), IFN beta-1a (Rebif), IFN beta-1b (Betaseron), and glatiramer (Copaxone) under the UF.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing IFN beta-1a (Avonex) on the ECF (18 for, 0 opposed, 0 abstained). MTFs may add additional MS-DMDs to their local formularies if needed to meet the needs of their specific patient populations. (See paragraph 10 E. on page 19 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

APPENDIX A – TABLE 1: PROCESSES AND RECOMMENDATION/APPROVAL AUTHORITIES

APPENDIX B – TABLE 2: NEWLY APPROVED DRUGS

APPENDIX C – DoD P&T COMMITTEE INTERIM MEETING: DERMATOLOGICAL TOPICAL ANTIFUNGAL DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the 11 dermatological topical antifungals marketed in the U.S. by considering information regarding their safety, tolerability, effectiveness, and other factors, including marketed formulations, generic availability, chemical structures, existing MHS utilization patterns, and Food and Drug Administration (FDA)-approved labeling. The dermatological topical antifungal class was defined as the "azoles" clotrimazole (various generics), econazole (various generics), ketoconazole (various generics), miconazole (various generics), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm); the "allylamines" butenafine (Mentax) and naftifine (Naftin); the "substituted pyridone" ciclopirox (Loprox); and the "polyene" nystatin. The topical formulation of terbinafine (Lamisil) was specifically excluded from the class, as it is now solely available in a non-prescription product.

A. COMMITTEE ACTION: The P&T Committee concluded that none of the topical antifungals have significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other topical antifungals. (See APPENDIX C, part A. on pages 23-24 of P&T Committee minutes for rationale). The P&T Committee concluded that econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole are not cost effective relative to nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine. (See APPENDIX C, part B. on pages 24-26 of P&T Committee minutes for rationale). Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness analysis of the topical antifungal agents, the P&T Committee voted (11 for, 1 opposed, 1 abstained) to recommend formulary status for nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine; and non-formulary status for econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole under the UF.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of econazole, sulconazole, ciclopirox, oxiconazole, sertaconazole, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended medical necessity criteria for econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole (12 for, 0 opposed, 1 abstained). (See APPENDIX C, part C. on page 26 of P&T Committee minutes for criteria)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because topical antifungal products are used to treat acute (rather than chronic) infections, patients are unlikely to require a change in existing therapy. For this reason the P&T Committee recommended (12 for, 0 opposed, 1 abstained) an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See APPENDIX C, part D. on page 26 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. *COMMITTEE ACTION:* Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing clotrimazole and nystatin on the BCF (12 for, 0 opposed, 1 abstained). MTFs may add additional UF topical antifungal agents to their local formularies if needed to meet the needs of their specific patient populations. (See APPENDIX C, part E. on pages 26-27 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

// William Winkenwerder, Jr.//
William Winkenwerder, Jr., M.D.
Date: 14 July 2005

Department of Defense
Pharmacy and Therapeutics Committee Minutes

19 May 2005

1. CONVENING

The DoD P&T Committee convened at 0800 hours on 17, 18, and 19 May 2005 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
MAJ Travis Watson, MS, USA	Director, DoD Pharmacy Programs, TMA
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Maj Charlene Reith, BSC (for Col Philip Samples, BSC)	Air Force, Pharmacy Officer
LtCol Brian Crownover, MC	Air Force, Physician at Large
CDR William Hall, MC (via VTC)	Navy, Internal Medicine Physician
LCDR Roger Akins, MC (via VTC)	Navy, Pediatrics Physician
CDR Brian Alexander, MC (via VTC)	Navy, Physician at Large
LCDR Joseph Lawrence, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Barry Sheridan, MC (for COL Joel Schmidt, MC)	Army, Physician at Large
COL Kent Maneval, MS (for COL Isaiah Harper, MS)	Army, Pharmacy Officer (Defense Medical Standardization Board)
CDR Vernon Lew	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS, USA	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx
Joe Canzolino (present May 17th only)	Department of Veterans Affairs

B. Voting Members Absent

None	

C. Non-Voting Members Present

Lynn Burleson	Deputy General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CDR William Blanche, MSC (present May 17th only)	Navy Pharmacy Specialty Leader
COL Gregory Wickern, MC	Air Force, Alternate for Pediatric Physician at Large
Mr. Dan Remund	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CAPT Donald Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col Barbara Roach, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss (present May 19th only)	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Col Nancy Misel, BSC, USAF	IMA, DoD Pharmacoeconomic Center
Mark Geraci (present May 18th only)	Department of Veterans Affairs
Paul Vasquez (present May 18th only)	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING

Dr. William Winkenwerder, Jr., M.D. approved the minutes of the DoD Pharmacy and Therapeutics (P&T) Committee held February 2005 on April 18, 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. The February 2005 DoD Pharmacy and Therapeutics Committee Minutes (Table 1: Process and Recommendations/Approval Authorities) - The P&T Committee developed a comprehensive list of functions associated with formulary management and categorized each in one of three decision processes outlined in Table 1 (Appendix A). Under 10 U.S.C. § 1074g and 32 C.F.R. 199.21, recommendations to the Director, TMA, on formulary status, preauthorizations, and the effective date for a drug's change from formulary to non-formulary status must be reviewed by the Beneficiary Advisory Panel (BAP) before the Director may make a final decision. Establishment and changes to

medical necessity criteria are not required to be reviewed by the BAP before the Director makes a final decision. An administrative clarification was made to the table as follows:

- **Approval by Director, TMA required based on DoD P&T Committee recommendations and BAP Comments**
  - Bullet: "Changes to the existing prior authorizations and medical necessity criteria (e.g., due to the availability of new efficacy or safety data)"
  - Was changed to: "Changes to existing prior authorizations (e.g., due to the availability of new efficacy or safety data)"
- **Approval by Director, TMA required based on Committee recommendations**
  - Bullet: "Establishment of medical necessity criteria for non-formulary agents"
  - Was changed to: "Establishment and changes to existing medical necessity criteria for non-formulary agents"

B. DoD P&T Committee Charter – Legal counsel stated that the wording of the DoD P&T Committee Charter is silent regarding the ability of alternate DoD P&T members to vote in the absence of the primary member. CAPT Buss stated that the following change to the charter has been proposed: Each voting member and non-voting member may have a designated alternate who can represent the member, including voting (if representing a voting member), at P&T Committee meetings in the event the member cannot attend.

C. Quantity Limit for Azelastine (Astelin) – Quantity limits for azelastine were set at the February 2005 DoD P&T meeting as 1 bottle per 30 days (retail), and 3 bottles per 90 days (mail order). The intent of the previous quantity limit was to provide 30-day increments of the medication under standard dosing regimens. However, because of priming requirements for initial and intermittent use, one bottle will not last for 30 days if used continuously under the standard dosing regime. Administrative adjustment of the azelastine quantity limits are as follows: 2 bottles per 30 days, 3 bottles per 60 days, and 4 bottles per 90 days. (ESI standard is 4 bottles per 90 days).

5. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD Pharmacoeconomic Center (PEC) staff members briefed the P&T Committee on the following:

A. Angiotensin Receptor Blocker (ARB) Drug Class Review Clarification: The P&T Committee's Uniform Formulary (UF) recommendations documented in the February 2005 minutes and approved by Dr. Winkenwerder include each of the listed ARBs and their respective combinations with hydrochlorothiazide. As a result, both eprosartan (Teveten) and eprosartan / hydrochlorothiazide (Teveten HCT) were designated as non-formulary under the UF, and both telmisartan (Micardis) and telmisartan / hydrochlorothiazide (Micardis HCT) were placed on the Basic Core Formulary (BCF).

B. Beneficiary Advisory Panel (BAP) Briefing: TMA briefed the members of the DoD P&T committee regarding the March 23, 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's UF and implementation recommendations.

C. Extension of Expiration Dates for Selected Agents Requiring Prior Authorization (PA): DoD PA criteria are currently established for agents within eight drug classes. These include: antifungals for onychomycosis [Lamisil (terbenafine), Penlac (ciclopirox), Sporanox (itraconazole)]; Enbrel (etanercept); fertility medications

(injectable gonadotropins); growth hormone (somatropin, somatrem); Humira (adalimumab); Kineret (anakinra); phosphodiesterase-5 (PDE-5) inhibitors [Cialis (tadalafil), Levitra (vardenafil), and Viagra (sildenafil)]; and Raptiva (efalizumab). When a PA is granted for any of these agents, the maximum duration of the PA is for one year.

Currently the contractor for TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy (TRRx) programs re-establishes the PA for each of these agents in these eight drug classes annually for the same fee that is negotiated for conducting the initial PA. Because the responses to the PA criteria established for some of these agents are not expected to change over time, re-establishing the PA for some of these agents annually will no longer be required, thus saving DoD the recurrent PA processing costs. As of June 1, 2005, these specific medications will no longer have a maximum one year expiration date and all existing PAs for them will have their current annual expiration date removed: Enbrel (etanercept); Humira (adalimumab); Kineret (anakinra); PDE-5 inhibitors (tadalafil, vardenafil, and sildenafil); and Raptiva (efalizumab).

D. Determining Medical Necessity for Non-Formulary Medications – PEC staff provided the DoD P&T Committee with an update concerning the medical necessity process for medications designated as non-formulary under the UF process. Important points included:

- Spouses, family members, and retirees do not need a medical necessity determination in order to fill prescriptions for non-formulary medications at the $22 non-formulary cost share through retail network pharmacies or mail order. They may fill prescriptions for non-formulary medications at the lower formulary cost share ($9) if the non-formulary medication is determined to be medically necessary.
- Active duty service members, who pay no cost shares, may not fill prescriptions for a non-formulary medication unless it is determined to be medically necessary. If the non-formulary medication is determined to be medically necessary, active duty service members may fill prescriptions at $0 cost share.
- Military Treatment Facilities (MTFs) will be able to fill non-formulary requests for non-formulary medications only if both of the following conditions are met: 1) a MTF provider writes the prescription, and 2) medical necessity is established for the non-formulary medication. MTFs may (but are not required to) fill a prescription for a non-formulary medication written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.
- Medical necessity criteria established by the DoD P&T Committee for medications designated as non-formulary under the UF apply to all three points of service (MTFs, mail order, retail). Medical necessity determinations are portable between the TMOP and the retail pharmacy network and have no expiration date.
- If an MTF fills a prescription for a medication designated as non-formulary under the UF process, the assumption is made that the MTF determined that it is medically necessary for the beneficiary to receive the non-formulary medication based on the criteria established by the DoD P&T Committee. An override is established in the patient's electronic medication profile and the beneficiary may then receive the non-formulary medication at the formulary cost share from either the retail pharmacy network or TMOP.
- According to the UF rule, information supporting medical necessity for use of a non-formulary medication may be provided at a later date (no later than 60 days

from the dispensing date), as an appeal to reduce the cost share for that prescription fill. Procedures are currently being developed to meet this requirement as of July 17, 2005, the effective date for the first medications designated as non-formulary under the UF process.

- More information, including medical necessity criteria and forms, is available on the TRICARE pharmacy website at: www.tricare.osd.mil/pharmacy/medical-nonformulary.cfm. Information on the formulary status and availability of specific medications is available by using the TRICARE Formulary Search Tool (www.tricareformularysearch.org).

E. PDE-5 Inhibitor PA Review – Mr. Dave Flowers presented a review of the status of the PDE-5 inhibitor PA with regard to frequency of requests, approval rate, and sentinel effect.

Frequency: At TRRx and TMOP, there were approximately 680 requests for PDE-5 PAs in the month of March 2005. This amount had been increasing slightly over the prior several months, gradually rising to this level from approximately 500 requests in the month of September 2004.

A significant reduction in the number of PA requests occurred beginning in mid-August 2004. From June 2004 through August 2004, an average of over 3,000 requests occurred each month. The reduction beginning in August was attributed to the automatic granting of PDE-5 inhibitor coverage to all males age 50 or over. This change was effective in Pharmacy Data Transaction Service (PDTS) on August 20, 2004, and as a result, no males age 50 or over have been required to follow the PA process in order to obtain these products.

***Approval* Rate:** Over the past ten months (June 2004 through March 2005), approximately 94% of all beneficiaries requesting PA for PDE-5 inhibitors were granted approval. When the PA requests were denied, there were three most commonly reported reasons. These reasons are presented below, in descending order of occurrence:

- PDE-5 is not being used for treatment of erectile dysfunction of organic origin
- PDE-5 is not being used for a male
- PDE-5 is not being used for the treatment of sexual dysfunction

Sentinel Effect: There are several measures that can be used to assess the impact of PA criteria. Frequency of occurrence, approval rate, and examining denial reasons are all common measures that represent components of a good approach to assess how many beneficiaries initiated the PA process, what was the eventual result, and why were these requests approved or denied.

An additional measure is assessing how many unique beneficiaries presented a prescription for a PDE-5 inhibitor in the TRRx and/or TMOP pharmacies, had this prescription rejected by PDTS at the point of service, and then chose not to initiate the formal PA approval process by submitting either the required forms, or having their provider contract the PA review team.

It was observed that there was a very large number of beneficiaries who elected to not initiate the necessary formal steps to obtain PA after receiving a rejection for a PDE-5 prescription at a TRRx or TMOP pharmacy.

The results for the first calendar quarter of 2005 (January through March 2005) are presented below:

- 5,176 = Beneficiaries with unique transaction rejects in PDTS requiring PA
- 1,829 = Beneficiaries entering the PA process
- 1,711 = Beneficiaries awarded a PA

6. REVIEW OF RECENTLY- APPROVED AGENTS

The PEC presented clinical information on three new medications approved by the FOOD AND DRUG ADMINISTRATION (FDA) and introduced to the U.S. market since February 2005 (Table 2 – Appendix B). Since none of the new medications fall into drug classes already reviewed by the P&T Committee, UF consideration was deferred until drug class reviews are completed.

The Committee discussed the potential need for a PA requirement for pramlintide (Symlin) subcutaneous injection, which presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for interaction with other medications, and required adjustment of insulin dosing due to the potential for severe hypoglycemia. The Committee agreed (11 for, 6 opposed, 2 abstained) that a PA recommendation should be considered for pramlintide and requested that the PEC develop PA criteria to be reviewed at the next meeting.

The Committee also discussed concerns regarding availability of pramlintide through the TMOP given the black box warning and safety issues, but agreed (9 for, 7 opposed, 3 abstained) that it should be available through the TMOP. The Committee requested more complete information about the manufacturer's plan to target use to appropriate patients, which was not available at the time of the meeting.

7. BCF CLARIFICATION OF RECENTLY APPROVED DRUGS

The DoD P& T Committee reviewed the relative clinical and cost effectiveness of the following recently approved formulations of medications already listed on the BCF.

A. Alendronate 70 mg /cholecalciferol (vitamin D) 2800 IU (Fosamax Plus D)

The current BCF listing for alendronate includes all oral strengths except 40 mg tablets, which are indicated only for the treatment of Paget's disease. Currently, the majority of use across DoD is the weekly formulations of alendronate (35- and 70-mg tablets). Addition of vitamin D, which is required for normal bone formation, to alendronate may provide a clinical advantage for patients who have inadequate dietary intake of vitamin D and insufficient exposure to sunlight. It is difficult to quantify this advantage, since many patients will also require supplemental calcium, which is readily available in combination with vitamin D. However, taking in account the manufacturer's offer to add alendronate plus D to the current BPA for alendronate without an increase in price and the fact that the product is not expected to delay the availability of generic versions of alendronate or alendronate plus vitamin D, the Committee agreed that the product offers a clinical advantage to MTF patients at no additional cost.

COMMITTEE ACTION: The Committee recommended adding alendronate plus D to the BCF (17 for, 1 abstained, 1 absent).

B. Fluticasone Propionate HFA (Flovent HFA)

The current BCF listing is for fluticasone oral inhaler. The manufacturer is no longer manufacturing the chlorofluorocarbon (CFC)-containing product (Flovent) and is

replacing it with a hydrofluoroalkane (HFA)-containing product (Flovent HFA). Since the product is now the only fluticasone metered dose inhaler available and since the HFA product does not appear to offer any clinical disadvantages compared to the CFC product, the Committee agreed that there was no need to clarify the current BCF listing. As of May 2005, the Flovent HFA metered dose inhaler was available to MTFs and TMOP at the same price as the old CFC formulation.

C. Insulin Glargine (Lantus) 100 u/mL 3 mL Cartridges

The current BCF listing is for insulin glargine injection (Lantus), which was previously available only as a 10 mL vial. The 3 mL cartridges are designed for use with the manufacturer's OptiClik device. The Committee agreed that while this device may benefit some patients (e.g., patients who are needle-phobic or visually impaired), the number of patients who would benefit represents only a small percentage of patients using insulin glargine. The Committee noted that, overall, about 92% of insulin use in DoD is vials, as compared to insulin pens, cartridges, and dispensing syringes which represent only 8% of use. The Federal Supply Schedule (FSS) price (as of May 2005) for Lantus was $25.70 for the 10 mL vial ($2.67 per mL) vs. $79.09 for a box of five 3 mL cartridges ($5.27 per mL). The Committee agreed that the potential clinical benefit associated with use of the cartridges was not sufficient to justify the additional cost.

COMMITTEE ACTION: The Committee recommended clarifying the current BCF listing for insulin glargine injection to exclude the 100 u/mL 3 mL cartridges (18 for, 1 abstained).

8. PHOSPHODIESTERASE (PDE-5) INHIBITOR DRUG CLASS REVIEW

A. **PDE-5 UF Clinical Effectiveness:** The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved PDE-5 inhibitors available in the U.S. The PDE-5 inhibitor therapeutic class was defined as sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The P&T Committee agreed that in the Military Health System (MHS) PDE-5s are considered to be the gold standard for the treatment of erectile dysfunction (ED). During a twelve month period ending January 31, 2005, 142,333 patients were prescribed a PDE-5 Inhibitor. This class is now ranked 46th in MHS drug class expenditures.

*1.) Efficacy: A*ll PDE-5 inhibitors have FDA approved indications for the treatment of ED. There are no head-to-head trials comparing the three PDE-5 inhibitors. The available placebo controlled trials and meta-analyses were reviewed. Although all PDE-5s were found to be clinically effective when compared to placebo, variability in study design, demographics, and outcome measures precluded the ability to designate one PDE-5 as clinically superior. A difference in duration of action exists among these agents. There is no evidence to suggest clinical superiority based on these differences. In addition to its FDA-approved indication for ED, sildenafil has also

been proven safe and effective for the treatment of primary pulmonary hypertension. Another off-label use of sildenafil is in the setting of radical prostatectomy, but there is not currently reliable evidence supporting its effectiveness for this indication.

2.) *Safety/Tolerability:* The P&T Committee found that the PDE-5 inhibitors were not significantly different with respect to major contraindications, drug interactions, and adverse drug reactions. As of May 2005 all agents have similar alpha-blocker warnings and nitrate contraindications. Vardenafil has a drug interaction warning associated with patients taking Class IA or Class III antiarrhythmics. Sildenafil is associated with more visual side effects where tadalafil is associated with more back pain.

Conclusion: The P&T Committee concluded that all PDE-5 inhibitors have similar relative clinical effectiveness for treating erectile dysfunction. All three PDE-5 inhibitors have similar safety and tolerability profiles.

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 1 abstained) that for the purposes of the UF clinical review, none of the PDE-5 inhibitors have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other PDE-5 inhibitors.

B. PDE-5 Inhibitor UF Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Several analyses were used to determine the relative cost effectiveness of agents within the PDE-5 inhibitor therapeutic class. A pharmacoeconomic analysis using cost minimization techniques was used based on the clinical review conclusion that the efficacy, safety, and tolerability between all agents were roughly equivalent. A series of cost effectiveness analyses were then conducted to confirm the results of the cost-minimization analysis. Cost effectiveness analyses were also used to evaluate differences in the duration of action between the agents.

Results of the cost minimization and cost effectiveness analyses (CMA/CEA) showed vardenafil to be the most cost effective PDE-5 inhibitor across all points of service (MTF, TRRx, TMOP). This was true even when taking into consideration differences in the duration of action between the agents.

The results of the above analyses were then incorporated into a budget impact analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of PDE-5 inhibitors within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA/CEA. Sildenafil and tadalafil were found not to be cost effective relative to vardenafil.

Conclusion: The P&T Committee concluded that sildenafil and tadalafil were not cost effective relative to vardenafil. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PDE-5 inhibitors, the P&T Committee recommended that the status of sildenafil and tadalafil be changed from formulary to non-formulary on the UF, with vardenafil maintaining formulary status on the UF with the formulary cost share.

COMMITTEE ACTION: The P&T Committee agreed (18 for, 0 opposed, 1 abstained) with the relative cost effectiveness analysis of the PDE-5 inhibitors presented. The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend non-formulary status on the UF for sildenafil and tadalafil, with vardenafil maintaining formulary status on the UF at the formulary cost share.

C. PDE-5 Inhibitor UF Medical Necessity Criteria: Based on the clinical evaluation of sildenafil and tadalafil, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for these agents.

1.) Use of the formulary PDE-5 inhibitor (vardenafil) is contraindicated, and the use of either sildenafil or tadalafil is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from the formulary PDE-5 inhibitor (vardenafil), and the patient is reasonably expected to tolerate either sildenafil or tadalafil.

3.) Use of the formulary PDE-5 inhibitor (vardenafil) resulted in therapeutic failure, and the patient is reasonably expected to respond to sildenafil or tadalafil [therapeutic failure as outlined on medical necessity form].

4.) The patient has previously responded to either sildenafil or tadalafil, and changing to vardenafil would incur unacceptable risk. This primarily pertains to patients requiring a PDE-5 inhibitor who have congenital or acquired QT prolongation or who are taking a Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarhrhythmic medication.

5.) Use of the PDE-5 inhibitor is for primary pulmonary hypertension and there is no alternative formulary agent.

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 0 abstained) to approve the medical necessity criteria.

D. PDE-5 inhibitor UF Implementation Plan: Because a substantial number of patients are currently receiving either sildenafil or tadalafil from one of the three MHS pharmacy points of service (128,007 patients, 90% of all patients receiving PDE-5 inhibitors) the P&T Committee proposed a 90-day transition period for implementation of the decision to change sildenafil and tadalafil to non-formulary drugs on the UF. Patients wishing to fill prescriptions for sildenafil or tadalafil at retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for these agents is established by the beneficiary or their provider.

MTFs will not be allowed to have sildenafil or tadalafil on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary provider must establish medical necessity for these agents. MTFs may (but are not required to) fill a prescription for sildenafil or tadalafil written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (17 for, 1 opposed, 1 abstention) an effective date no later than the first Wednesday following a 90-day

implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. PDE-5 Inhibitor Extended Core Formulary (ECF) Review and Recommendations: The P&T Committee had previously determined that only one PDE-5 inhibitor would be added to the ECF based on the clinical and cost effective reviews. Since only one PDE-5 inhibitor, vardenafil, was selected for UF status, it was recommended that this agent also be added to the ECF.

Conclusion: Vardenafil was recommended for inclusion on the ECF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend that vardenafil be on the ECF.

9. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR DRUG CLASS REVIEW

The DoD P&T Committee initiated the ACE inhibitor class review; however because price submissions were not complete, no action was taken. Two ACE inhibitors, available as multisource generics for approximately two years, recently suspended manufacturing secondary to litigation results. The Committee will seek pricing information from the companies representing the name brand version of these products. Continuation of the ACE inhibitor review will occur at the August 2005 DoD P&T Committee meeting.

10. MULTIPLE SCLEROSIS DISEASE MODIFYING DRUG (MS-DMD) CLASS REVIEW

A. MS-DMDs UF Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the four MS-DMDs in the U.S. by considering information regarding their safety, effectiveness and clinical outcomes. Currently, MS-DMDs have been approved for the treatment of relapsing-remitting (RR) MS. The therapeutic class includes three interferons (IFN): intramuscular (IM) IFN beta-1a (Avonex), subcutaneous (SC) IFN beta-1a (Rebif), SC IFN beta-1b (Betaseron); and one subcutaneous (SC) polypeptide mixture, glatiramer acetate (Copaxone). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

MS-DMDs have been available for the past 12 years and the class is currently ranked 33rd in MHS drug class expenditures. During a twelve-month period ending January 31, 2005, approximately 6,500 patients were prescribed a MS-DMD. In most cases MS-DMDs are prescribed by sub-specialists (neurologists).

1.) Efficacy for RR-MS: All the IFNs and glatiramer are indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations. Avonex and Rebif also claim to delay accumulation of physical disability. A Cochrane systematic review of all the available trials through 2000 found only a modest reduction in exacerbations and disability following treatment of RR-MS with IFNs. A Cochrane systematic review of trials available through 2003 concluded that glatiramer had a modest reduction in exacerbations, but no beneficial

effect on disease progression. A decrease in exacerbations does not necessarily correlate to the progression of disease. There is no compelling evidence to support superiority of one agent over another. All beta IFNs and glatiramer have been shown to have a modest protective effect on disease exacerbations. IFN beta-1a agents (Rebif and Avonex) have shown to have a modest protective effect on disease disability; therefore they may have a marginal benefit over glatiramer.

2.) Safety/Tolerability: The P&T Committee agreed that there is no evidence that any one MS-DMD is preferable to the others with respect to safety or tolerability. These medications are generally well-tolerated and adverse events are dose-related. The most common side effects were local injection site reactions for the SQ drugs and flu-like symptoms for the IM drugs. Additionally, a self-limiting allergic-type reaction may be seen with glatiramer. All the MS-DMDs have similar safety and tolerability profiles with only rare incidences of true serious adverse effects.

Conclusion: The P&T Committee concluded that there is no compelling evidence to support superiority of one MS-DMD agent over another in the treatment of RR-MS. All MS-DMD agents have shown a modest effect in reducing exacerbations, with IFN beta-1a agents (Rebif and Avonex) demonstrating a modest reduction on disease disability. All the IFNs and glatiramer have similar safety and tolerability profiles.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (18 for, 0 opposed, 0 abstained) to accept the conclusion that none of the MS-DMDs have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other MS-DMDs.

B. MS-DMD UF Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2).

Cost-minimization techniques determined that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex, followed by Copaxone and Betaseron. Rebif was determined to have the highest average weighted cost per treatment day.

Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MS-DMDs, and other relevant factors (i.e., relative uniqueness of each agent in patient therapy and the low expectation that patient behavior would be affected by formulary status), the P&T Committee recommended that all MS-DMDs [IFN beta-1a (Avonex), IFN beta-1a (Rebif), IFN beta-1b (Betaseron), and glatiramer acetate (Copaxone)] maintain UF status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (18 for, 0 opposed, 0 abstained) to recommend formulary status for IFN beta-1b (Betaseron), IFN beta-1a (Avonex), IFN beta-1a (Rebif), and glatiramer (Copaxone) under the UF.

C. MS-DMD UF Medical Necessity Criteria: Since no agents were selected for non-formulary status on the UF, establishment of medical necessity criteria is not applicable.

D. MS-DMD UF Implementation Plan: Since no agents were selected for non-formulary status on the UF, establishment of an implementation plan is not applicable

E. MS-DMD ECF Review and Recommendations: The P&T Committee had previously determined that this class of drugs is more suitable for ECF due to the subspecialty nature of the MS-DMD class. The P&T Committee reviewed the MS-DMDs recommended for inclusion on the UF to select one MS-DMD for inclusion on the ECF. Cost-minimization techniques determined that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex. PDTS data collected from October 1, 2001 to March 30, 2005 showed that Avonex has maintained the highest percent of MTF market share of all MS-DMDs. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing Avonex on the ECF.

Conclusion: The P&T Committee concurred with the recommendation to place Avonex on the ECF based on its high MTF utilization and cost effectiveness

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 0 abstained) to recommend Avonex as the ECF agent.

11. ADJOURNMENT

The third day of the meeting adjourned at 1100 hours on May 19, 2005. The dates of the next meeting are August 16–18, 2005.

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Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Processes and Recommendation/Approval Authorities

Process	Function
Administrative (not part of DoD P&T Committee process, Beneficiary Advisory Panel (BAP) comments not required, Director, TMA, approval not required) Responsible parties include: TRICARE Mail Order Pharmacy and TRICARE Retail Pharmacy Contracting Officer Representatives (TMOP and TRRx CORs), TMA Pharmacy Program, TMA Office of General Counsel, and Pharmacoeconomic Center (PEC) staff	▪ Identification of new FDA-approved medications, formulations, strengths, package sizes, etc. ▪ If situation unclear, determination as to whether a new FDA-approved medication is covered by TRICARE ▪ If situation unclear, determination as to whether a new FDA-approved medication is part of the pharmacy benefit ▪ If situation unclear, determination as to whether a new FDA-approved medication is suitable for dispensing through the TRICARE Mail Order Pharmacy (TMOP) ▪ Calculating and implementing quantity limits if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making changes to quantity limits as needed based on non-clinical factors such as changes to packaging (e.g., medication previously available in boxes of 5 now only available packaged in boxes of 8) ▪ Establishing adjudication edits (PDTS limitations which are set well above the clinical maximum and are intended to prevent entry errors [e.g., entering a quantity of 17 for a 17-gram inhaler for which the actual unit of measure is 1 inhaler] or are intended to limit diversion) ▪ Implementing prior authorization requirements if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making minor changes to prior authorization forms NOT involving changes to underlying criteria, such as correcting contact information or rewording clinical questions ▪ Making changes to PA criteria, medical necessity criteria, quantity limits and any associated documents to accommodate new FDA-approved indications or respond to changes in FDA-recommended safety limitations (changes will be reviewed by DoD P&T Committee at next meeting) ▪ Removing medications withdrawn from the U.S. market from Basic Core Formulary (BCF) or Extended Core Formulary (ECF) listings and other documents ▪ Providing clarifications to existing listings on the BCF or ECF to specify specific brands/manufacturers when a joint DoD/VA mandatory source generic contract is awarded for a given product (i.e., clarifying an existing listing for “atenolol” to include the contractual requirement to use a specific manufacturer’s products) ▪ As necessary to accomplish functions above: for example, making changes to PDTS coding for TMOP & TRRx, communicating status of medications as part of the pharmacy or medical benefit to Managed Care Support Contractors (MCSCs), making changes to the TMA Pharmacy website and the TRICARE Formulary Search Tool, and making changes to BCF and ECF listings on the PEC website.
Approval by Director, TMA, required based on DoD P&T Committee recommendations and BAP comments	▪ Classification of a medication as non-formulary on the Uniform Formulary (UF), and implementation plan (including effective date) ▪ Establishment of prior authorization requirement for a medication or class of medications, summary/outline of prior authorization criteria, and implementation plan (including effective date) ▪ Changes to existing prior authorization (e.g., due to the availability of new efficacy or safety data) ▪ Discontinuation of prior authorization requirements
Approval by Director, TMA, required based on DoD P&T Committee recommendations (not required to be submitted to BAP for comments)	▪ Establishment of quantity limits for a medication or class of medications; deletion of existing quantity limits; changes to existing quantity limits based on clinical factors (e.g., new clinical data or dosing regimens) ▪ Establishment and changes of medical necessity criteria for non-formulary agents ▪ Addition, deletion of medications listed on the Basic Core Formulary (BCF) or Extended Core Formulary (ECF)

Appendix B – Table 2. Newly Approved Drugs

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Pramlintide (Symlin; Amylin Pharm) injection; synthetic version of the neuro-endocrine hormone amylin, which complements the action of insulin by decreasing post-prandial glucose levels and slowing gastric emptying	Mar 05: *Type 1 DM*: as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy *Type 2 DM*: as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin Should be considered only for patients who have failed to achieve adequate glycemic control despite individualized insulin management and are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin and supported by the services of a diabetes educator. Should NOT be considered for treatment of patients in the following categories: poor compliance with current insulin regimen; poor compliance with prescribed self-blood glucose monitoring; HbA1c >9%; recurrent severe hypoglycemia requiring assistance during the past 6 months; presence of hypoglycemia unawareness; confirmed diagnosis of gastroparesis; requirement for drugs that stimulate gastrointestinal motility; pediatric patients.	Prior authorization recommended due to safety concerns and the existing FDA requirements for risk minimization. Consideration of UF status deferred until drug class is reviewed.
Ibandronate Na (Boniva; Roche/GSK) 150 mg q month tabs; bisphosphonate; inhibits bone resorption	Mar 05: Treatment and prevention of osteoporosis in postmenopausal women	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Eszopiclone (Lunesta: Sepracor) tabs (control schedule IV); non-benzodiazepine sedative hypnotic	Dec 04: Treatment of insomnia. In controlled outpatient and sleep laboratory studies, Lunesta administered at bedtime decreased sleep latency and improved sleep maintenance	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – DoD P&T Committee Interim Meeting: Topical Antifungal Drug Class Review

The P&T Committee held an interim electronic meeting during the period June 3, 2005 through June 6, 2005, during which it completed the class review that had been initiated during the May meeting of the Committee. A quorum of thirteen Committee voting members participated.

DERMATOLOGICAL TOPICAL ANTIFUNGAL DRUG CLASS REVIEW

A. Topical Antifungal UF Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the 11 dermatological topical antifungals marketed in the US by considering information regarding their safety, tolerability, effectiveness, and other factors, including marketed formulations, generic availability, chemical structures, existing MHS utilization patterns, and FDA-approved labeling. The dermatological topical antifungal class was defined as the "azoles" clotrimazole (various generics), econazole (various generics), ketoconazole (various generics), miconazole (various generics), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm); the "allylamines" butenafine (Mentax) and naftifine (Naftin); the "substituted pyridone" ciclopirox (Loprox); and the "polyene" nystatin. The topical formulation of terbinafine (Lamisil) was specifically excluded from the class, as it is now solely available in a non-prescription product. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1.) *Other Factors: Structure/Mechanism of action:* The Committee agreed that it would be advantageous to include on the UF products that are available in more than one formulation, products that have differing mechanisms of action (e.g., an allylamine and an azole), products that have a wide number of FDA-approved indications, and products that are approved for use in the pediatric population.

2.) *Efficacy for tinea pedis:* A Cochrane systematic review for treatment of tinea pedis infections reported that allylamines were slightly more efficacious than the azoles; however, there was a language bias present, and the overall cure rates were similar (80% cure rates with the allylamines vs. 73% with the azoles). Ciclopirox showed similar efficacy as clotrimazole. There was no difference in cure rates when azoles were compared to azoles, or when allylamines were compared to allylamines. Three topical antifungals were not included in the Cochrane review: ketoconazole, oxiconazole and sertaconazole. The cure rates reported in clinical trials with use of ketoconazole for tinea pedis are similar to those reported with the other azoles. Head-to-head trials comparing ketoconazole shampoo to ciclopirox shampoo for treating seborrheic dermatitis reported no differences in efficacy. Head-to-head trials of oxiconazole to naftifine and terbinafine show similar efficacy. Cure rates reported

with sertaconazole were low (30%) in the clinical trials used to gain FDA approval; however the FDA now has more stringent requirements for definitions of mycological cure than were used previously. Overall, there is no evidence to support that one individual topical antifungal agent is superior to another for treating tinea pedis.

3.) *Efficacy for tinea cruris, tinea corporis, or pityriasis versicolor*: There are no systematic reviews and no head-to-head trials of individual topical antifungal agents for treating tinea cruris, tinea corporis or pityriasis versicolor. There is no evidence that any one topical antifungal agent is superior to another for treating these conditions.

4.) *Efficacy for cutaneous candidiasis*: There are no systematic reviews for the treatment of cutaneous candidiasis. Two head-to-head trials comparing nystatin to miconazole and nystatin to tolnaftate showed similar efficacy. There is no evidence that any one topical antifungal agent is superior to another for treating cutaneous candidiasis.

5.) *Safety/Tolerability*: The topical antifungals are recognized as safe therapeutic agents. Several of the products (clotrimazole, miconazole, butenafine) are available without a prescription in the same concentration and dosage form as the prescription product. Hypersensitivity is the only contraindication listed in the package inserts of the topical antifungals. Adverse reactions reported most commonly with the topical antifungals include itching, burning, and erythema, which are the common symptoms of fungal infections. Adverse event rates listed in the individual agents' product labeling range from 1-3%. Products containing propylene glycol may cause burning, but this varies with the dosage form and type of infection being treated.

Conclusion: The Committee concluded that the topical antifungals have similar safety and tolerability profiles. The individual topical antifungal agents appear to have similar efficacy and clinical outcomes for treating tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor, and cutaneous candidiasis infections. Differences do exist in such factors as existing MHS utilization, available formulations, FDA-approved indications, pediatric labeling and dosing duration.

COMMITTEE ACTION: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend that, for the purposes of the UF, none of the topical antifungals have significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other topical antifungals. The UF recommendation can be based on cost, current utilization patterns, available formulations, pediatric indications, and dosing duration. The Committee also recommended having agents with differing mechanisms of action (azoles and allylamines) on the UF. The FDA-approved indications, clinical use, and dosing duration of ciclopirox is more similar to that of the azoles, rather then the allylamines; thus for cost effectiveness determinations, ciclopirox was considered along with the azoles.

B. Topical Antifungal UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost effectiveness of the agents within the topical antifungal class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost effectiveness of the agents within the topical antifungal therapeutic class, two separate

economic analyses were performed: A pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee agreed that there was no compelling evidence to support clear superiority of one agent over another in terms of safety, effectiveness or clinical outcomes. For the UF, it would be advantageous to include products with differing mechanisms of action (e.g., an allylamine and an azole), those available in multiple dosage formulation, those approved for use in the pediatric setting, and those with existing high utilization in the MHS. The clinical characteristics of the substituted pyridone ciclopirox are more closely related to the azole topical antifungals than the allyalmines. For the purposes of the relative clinical effectiveness evaluation, topical antifungals with the azole and substituted pyridone (ciclopirox) structure were analyzed collectively; those agents with an allylamine structure were also analyzed separately from the azoles/substituted pyridone.

Given this conclusion, two cost-minimization analyses (CMAs) were conducted for each sub-class using two different measures of cost; the weighted average cost per gram and the weighted average annual cost of treatment per unique user. In general, the results of the CMAs revealed that: miconazole was the most cost effective agent in the azole/ substituted pyridone sub-class; naftifine and butenafine were similar in relative cost effectiveness in the allylamine sub-class; and nystatin was the most cost effective agent relative to all topical antifungals. More specifically, within the allylamine sub-class, naftifine was more cost effective than butenafine at the MTF and TMOP point of service (POS), whereas butenafine was more cost effective relative to naftifine at the TRRx POS. Examination of the cost continuum further suggested that a cluster of agents (nystatin, miconazole, clotrimazole, and ketoconazole) were more cost effective relative to the other agents within the therapeutic class (butenafine, ciclopirox, econazole, naftifine, oxiconazole, sertaconazole, and sulconazole). The results of the CMA were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that the status of one or more topical antifungals be changed from formulary to non-formulary such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to identify a group of antifungal agents to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS, given the DoD P&T Committee's decision to include on the UF at least one-agent from the azole/substituted pyridone sub-class, one agent from the allylamine sub-class, and nystatin. The BIA results revealed that a group of topical antifungals comprising nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine best achieved this goal when compared to other combination groups of antifungals, and thus this group was determined to be more cost effective relative to other combination groups. The P&T Committee concluded that ciclopirox, econazole, oxiconazole, sertaconazole, and sulconazole were not cost effective relative to the other topical antifungals.

Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the topical antifungals, the P&T Committee recommended that the status of econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole be changed from formulary to non-formulary, with

butenafine, clotrimazole, ketoconazole, miconazole, naftifine, and nystatin maintaining formulary status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee agreed (12 for, 0 opposed, 1 abstained) with the relative cost effectiveness analysis of the topical antifungal agents presented. The P&T Committee, based upon its collective professional judgment, voted (11 for, 1 opposed, 1 abstained) to recommend formulary status for nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine, and non-formulary status for ciclopirox, econazole, oxiconazole, sertaconazole, and sulconazole under the UF.

C. Medical Necessity Criteria: Based on the clinical evaluation of the topical antifungals and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the following medical necessity criteria were proposed for the non-formulary topical antifungals.

1.) Use of the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin) is contraindicated, and the use of the non-formulary topical antifungal is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from all the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin), and the patient is reasonably expected to tolerate the non-formulary topical antifungal.

3) Use of the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin) resulted in therapeutic failure following administration for the appropriate duration of therapy (2 weeks for an allylamine and 4 weeks for an azole), and the patient is reasonably expected to respond to the non-formulary topical antifungal.

4.) The criterion that "the patient has previously responded to a non-formulary topical antifungal, and changing to a formulary topical antifungal would incur unacceptable risk" does NOT apply to this class as there are few safety concerns with topical antifungals, treatment is usually well tolerated, and therapy is generally limited to single treatment courses.

5) The criterion that "there are no formulary alternatives" does NOT apply to this class, as six topical antifungals are recommended for inclusion on the UF.

COMMITTEE ACTION: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend the medical necessity criteria for the non-formulary topical antifungals.

D. Implementation Plan: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend an effective date of the first Wednesday after 30 days from the final decision date (the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation). A 30-day implementation period is recommended, since the topical antifungal products are used to treat acute (rather than chronic) infections, thus patients are unlikely to require a change in existing therapy.

E. Topical Antifungal BCF Review and Recommendations: The P&T Committee reviewed the topical antifungals recommended for inclusion on the UF to select the BCF topical antifungals. It had previously been decided that at least two, but no more than

three topical antifungals, could be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

There are currently no topical antifungal products on the BCF. Since no BCF prices were submitted for any of the topical antifungals, the DoD P&T Committee evaluated the relative cost effectiveness for BCF selection based on the cost effectiveness information provided for the UF formulary recommendation. Although the CMA revealed that miconazole (#4 in utilization at the MTF at 2,000 Rxs/month) was more cost effective than clotrimazole, the difference was determined to be negligible. From a clinical and economic standpoint, clotrimazole is a rational selection for the BCF due to its wide number of FDA-approved indications (tinea pedis, tinea cruris, tinea "pityriasis" versicolor, and cutaneous candidiasis), availability in several formulations (cream, lotion, topical solution), pediatric labeling in children older than 2 years of age, and high utilization in the MHS (#1 in utilization at the MTFs at 11,000 Rxs/month). Nystatin is also recommended for BCF selection due to its availability in several formulations (cream, ointment, powder), widespread usage for cutaneous candidiasis, rapid symptomatic relief, popularity of the powder dosage form, and high utilization (#3 in MTFS at 4,500 Rxs/month). Ketoconazole is #2 in MTF utilization, the CMA revealed it to be less cost effective than clotrimazole, and there is no therapeutic rationale to include two azoles on the BCF. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing clotrimazole and nystatin on the BCF. MTFs can add additional UF topical antifungals to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place clotrimazole and nystatin on the BCF.

COMMITTEE ACTION: The P&T Committee voted (12 for, 0 opposed, 1 abstained) to recommend clotrimazole and nystatin as the BCF agents.

16 February 2005

DECISION PAPER:

FEBRUARY 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

5. ITEMS FOR INFORMATION

6. DRUG REVIEW PROCESS

Implementation of the Uniform Formulary (UF) entails a wide variety of actions, with various levels of involvement of the DoD Pharmacy and Therapeutics (P&T) Committee, the Beneficiary Advisory Panel (BAP), and the Director, TRICARE Management Activity (TMA). However, not all of these actions require comment by the BAP, or recommendations or action by the P&T Committee or final decision by the Director, TMA, before they can be implemented. The P&T Committee developed a comprehensive list of the functions associated with formulary management and categorized each into one of three decision process categories, depending on the level of involvement for the P&T Committee, BAP, and/or Director, TMA.

COMMITTEE ACTION: Functions/actions of the Committee were reviewed and categorized according to the following processes: administrative functions (day-to-day maintenance not requiring DoD P&T Committee review), formulary recommendations requiring DoD P&T Committee review and approval by the Director, TMA, and formulary changes requiring DoD P&T Committee review and approval of the Committee's recommendations by the Director, TMA, after considering comments from the BAP. (See paragraph 6 and Table 1 on pages 13-14 of P&T Committee minutes.)

Recommendation: The Committee recommended approval of functions and decision categories as described.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows

7. PRIOR AUTHORIZATIONS

The P&T Committee reviewed existing prior authorizations (PAs) and recommended rules for agents that are approved by the Food and Drug Administration (FDA) between Committee meetings that are in therapeutic classes for which PAs already exist.

COMMITTEE ACTION: The Committee discussed how to apply existing drug class PAs to newly FDA-approved drugs in within the class. (See paragraph 7 on pages 14-15 of P&T Committee minutes.)

The Committee recommended the following:

- Phosphodiesterase-5 (PDE-5) inhibitors – Any new PDE-5 inhibitor that may become available for the treatment of erectile dysfunction will be subject to the same PA as the existing agents.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

- Injectable gonadotropins – Any new injectable gonadotropin that may become available for infertility treatment will be subject to the same PA as the existing agents.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

- Antifungals for onychomycosis – Any new oral or topical antifungal that may become available for the treatment of onychomycosis will be subject to the same PA as the exiting agents, with course of therapy limits set based on recommended dosing.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

- Growth hormone agents – Any new growth hormone agent that may become available will be subject to the same PA as the existing agents.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

8. QUANTITY LIMITS

The P&T Committee reviewed all current quantity limits (QLs) with the intention to recommend any necessary additions, deletions, or changes, and to formulate and recommend rules for those QLs that apply to groups of medications, including new medications or formulations as soon as they become available. The P&T Committee's goal is to ensure a consistent benefit and avoid circumstances under which a newly approved medication, very similar to another medication for which a QL exists, is on the UF for several months of unrestricted use before a QL can be applied. The PEC would report changes to QLs following these general rules at the next scheduled DoD P&T Committee meeting.

A. COMMITTEE ACTION: The P&T Committee recommended the establishment of general QL rules for the following groups of medications (see paragraph 8 on page 15-16 of P&T Committee minutes and Appendix A for the rationale):

- Medications for the treatment of erectile dysfunction (PDE-5 inhibitors and injectable/intraurethral prostaglandins)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- 5-HT3 receptor antagonists (antiemetic medications)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- 5HT-1 receptor agonists ("triptans") for the treatment of migraine

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Dihydroergotamine products for the treatment of migraine

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Fertility agents (injectable gonadotropins)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Nasal inhalers for the treatment of allergic and nonallergic rhinitis

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Oral inhalers and inhalant solutions for the treatment of asthma, chronic obstructive lung disease, or allergies

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Tramadol-containing products

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows

B. COMMITTEE ACTION*:* The P&T Committee recommended the following specific changes to QLs (see paragraph 8 on page 16 of P&T Committee minutes and Appendix A for the rationale):

- Dihydroergotamine nasal spray (Migranal) – change to 16 amps per 30 days; 48 amps per 90 days)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

C. COMMITTEE ACTION*:* The Committee recommended the establishment of QLs for newly-approved agents: (See paragraph 8 on page 16 of P&T Committee minutes and Appendix A for the rationale):

- Azelastine nasal spray (Astelin) – 1 bottle per 30 days or 3 bottles per 90 days

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Tazarotene (Tazorac) cream – 60 gm (1 large tube) per 30 days; 180 gm per 90 days

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows

D. COMMITTEE ACTION*:* The P&T Committee recommended the deletion of QLs: (See paragraph 8 on pages 16-17 of P&T Committee minutes and Appendix A for the rationale):

- Azithromycin (Zithromax) 250- and 600-mg tablets

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Dornase alpha inhalation solution (Pulmozyme)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows

- Fluconazole (Diflucan, generics) 150 mg tablets

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Imiquimod cream (Aldara)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows

- Testosterone buccal system (Striant)

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows

9. REVIEW OF RECENTLY-APPROVED DRUGS

The P&T Committee was briefed on agents who had been approved by the FDA and introduced into the U.S. market since the July 2004 meeting. None of the new medications fall into drug classes already reviewed by the P&T Committee; therefore, the P&T Committee deferred UF consideration until the applicable drug class reviews are completed.

COMMITTEE ACTION*:* The Committee recommended quantity limits for the following products (see paragraph 9 on page 17 of P&T Committee minutes and Appendix B for the rationale):

- Erlotinib tabs (Tarceva) – limit of 30 day supply in retail, 45 day supply in TRICARE Mail Order Pharmacy (TMOP) Program, up to 45 day supply in MTFs. No multiple fills for multiple co-pays in retail and TMOP

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

- Gemifloxacin tablets (Factive) – limit of 7 days supply per 30 days in retail, TMOP and MTFs

*Director, TMA, Decision***:** □ Approved □ Disapproved
□ Approved, but modified as follows:

10. BASIC CORE FORMULARY (BCF) ISSUES

The DoD P&T Committee reviewed the relative clinical and cost effectiveness of timolol maleate ophthalmic solutions and gels, which had previously been placed on the BCF. MTFs are advised that the BCF listing for timolol maleate products relates to the product for which DoD has a sole source contract, and does not include the Istalol brand of timolol maleate ophthalmic solution.

11. ANGIOTENSIN RECEPTOR BLOCKER (ARB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs): losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar), and included their respective combinations with hydrochlorothiazide. There has been an increase in the use of ARBs over the past five years, and the class is now in the top 10 of Military Health System (MHS) drug class expenditures.

A. COMMITTEE ACTION: The Committee concluded that (1) all seven ARBs have similar relative clinical effectiveness for treating hypertension; (2) that candesartan and valsartan have similar relative clinical effectiveness for treating chronic heart failure; (3) that losartan and irbesartan have similar relative clinical effectiveness for treating Type 2 diabetics with nephropathy; and (4) that all seven ARBs have similar safety and tolerability profiles. Valsartan, candesartan, losartan and irbesartan have higher clinical utility (overall clinical usefulness) relative to the three ARBs that are indicated solely for treating hypertension (telmisartan, eprosartan, and olmesartan). (See paragraph 11 A. on pages 18-19 of P&T Committee minutes.) The P&T Committee concluded that eprosartan was not cost-effective relative to the other ARBs for treating hypertension. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee voted to recommend formulary status for candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, and non-formulary status for eprosartan under the UF. (See paragraph 11 B. on page 20 of P&T Committee minutes.) Under 32 C.F.R. 199.21(g)(3), no pharmaceutical agent may be designated as non-formulary on the UF unless preceded by such recommendation by the P&T Committee.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of eprosartan, and the conditions for establishing medical necessity for a non-formulary medication provided for in the Uniform Formulary rule, the P&T Committee recommended medical necessity criteria for eprosartan. (See paragraph 11 C. on pages 20-21 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

C. COMMITTEE ACTION: Because relatively few patients are receiving eprosartan at any MHS pharmacy point of service (less than 1% of all patients receiving ARBs), the P&T Committee recommended an effective date of 30 days from the final decision date (the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation). (See paragraph 11 D. on page 21 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

D. COMMITTEE ACTION: Within the MTFs, the majority of ARB usage is for treating hypertension, and not for treating chronic heart failure or Type 2 diabetic nephropathy. Although valsartan, candesartan, irbesartan, and losartan have additional indications, which are of importance in the UF at the MTF setting, selecting one BCF ARB with a sole indication for hypertension is sufficient to meet the needs of the majority of patients. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing telmisartan on the BCF. MTFs can add additional ARBs to their local formularies if needed to meet the needs of their specific patient populations. (See paragraph 11 E. on pages 21-22 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

12. PROTON PUMP INHIBITOR (PPI) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved proton pump inhibitors (PPIs) available in the US: omeprazole (Prilosec, Zegerid & generics), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix) and esomeprazole (Nexium). PPIs are among the top 10 MHS drug class expenditures.

A. COMMITTEE ACTION*:* The P&T Committee concluded that all PPIs have similar relative clinical effectiveness for treating gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). All five PPIs have similar safety and tolerability profiles. (See paragraph 12 A. on paged 22-23 of P&T Committee minutes for the rationale). The P&T Committee concluded that esomeprazole was not cost effective relative to the other PPIs. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs and other relevant factors, the P&T Committee voted to recommend non-formulary status for esomeprazole, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status with a formulary cost share, and omeprazole maintaining formulary status with a generic cost share. (See paragraph 12 B. on page 23 of P&T Committee minutes for the rationale.) Under 32 C.F.R. 199.21(g)(3), no pharmaceutical

agent may be designated as non-formulary on the UF unless preceded by such recommendation by the P&T Committee.

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of esomeprazole, and the conditions for establishing medical necessity for a non-formulary medication provided for in the Uniform Formulary rule, the P&T Committee recommended medical necessity criteria for esomeprazole. (See paragraph 12 C. on pages 23-24 of P&T Committee minutes for the criteria.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

C. COMMITTEE ACTION: Based on the substantial number of patients currently receiving esomeprazole from one of the three MHS pharmacy points of service (138,739 patients, or 13.4 % of all patients receiving PPIs), the P&T Committee recommended an implementation date of 90 days from the final decision date (the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation). (See paragraph 12 D. on page 24 of P&T Committee minutes for the rationale.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost-effectiveness, the P&T Committee recommended placing omeprazole (generic) and rabeprazole (Aciphex) on the BCF. However, omeprazole suspension (Zegerid) and Prilosec 40 mg were excluded from the BCF, because they were less cost-effective than the generic omeprazole. (See paragraph 12 E. on pages 24-25 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** □ Approved □ Disapproved

□ Approved, but modified as follows:

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

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William Winkenwerder, Jr., M.D.
Date:

Department of Defense
Pharmacy and Therapeutics Committee Minutes

16 February 2005

1. CONVENING

The DoD P&T Committee convened at 0800 hours on 15 and 16 February 2005 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC	DoD P& T Committee Chair
CDR Mark Richerson, MSC	DoD P& T Committee Recorder
Col James Young, BSC	Director, DoD Pharmacy Programs, TMA
Capt Michael Proffitt, MC (present Feb 15th only)	Air Force, OB/GYN Physician
Maj Nick Conger, MC	Air Force, Internal Medicine Physician
Maj Charlene Reith, BSC (for Col Phil Samples, BSC)	Air Force, Pharmacy Officer
CDR William Hall, MC	Navy, Internal Medicine Physician
LCDR Suzanne Haney, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
CDR Ted Briski, MSC (for LT Joseph Lawrence, MSC)	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
COL Isiah Harper, MS	Army, Pharmacy Officer
CDR Mary Fong (for CDR Patrick Marshall)	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC	Contracting Officer Representative, TRRx
Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

Maj Brian Crownover, MC	Air Force, Physician at Large

C. Non-Voting Members Present

Howard Altschwager	Deputy General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
Capt Peter Trang, BSC	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

COL Kent Maneval, MS	Joint Readiness Clinical Advisory Board

E. Others Present

CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
CDR Bill Blanche, MSC	Future Navy Pharmacy Specialty Leader
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CAPT Don Nichols, MC	DoD Pharmacoeconomic Center
Lt Col Dave Bennett, BSC	DoD Pharmacoeconomic Center
Lt Col Barb Roach, MC	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
Col Nancy Misel, BSC	IMA, DoD Pharmacoeconomic Center
Todd Semla	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

Dr. William Winkenwerder, Jr., M.D. approved the minutes of the first meeting of the restructured DoD Pharmacy and Therapeutics (P&T) Committee held July 2004 on October 5, 2004.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

None.

5. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD Pharmacoeconomic Center (PEC) staff members briefed the P&T Committee on the following:

A. The TRICARE Pharmacy Benefit Program Formulary Management Policy (HA Policy 04-032) was signed by Dr. Winkenwerder on December 22, 2004. This new HA Policy addresses how formulary management in the Military Health System (MHS) is accomplished by the DoD P&T Committee through the Uniform Formulary (UF), the Basic Core Formulary (BCF), and the Extended Core Formulary (ECF). Formulary

management by the Services and individual Military Treatment Facilities (MTFs) is limited to the circumstances described in this policy.

B. Quantity Limits, Prior Authorizations, and Medical Necessity Criteria – 10 U.S.C. § 1074g requires the establishment of an effective, efficient, integrated pharmacy benefit program under chapter 55 of title 10, United States Code, which applies to MTFs as well as to the purchased care system. The DoD P&T Committee makes recommendations to the Director, TMA, not only on formulary/non-formulary status for pharmaceutical agents in a class, but also on prior authorizations, quantity limits, and medical necessity criteria. Therefore, prior authorizations, quantity limits, and medical necessity criteria established by the DoD P&T Committee will apply to all three points of service.

C. Review of Medications for the Uniform Formulary – The Director, TMA, directed the implementation of the UF as a phased-in approach, one class at a time. Operating rules of the UF will only be applicable for those drug classes already evaluated by the DoD P&T Committee. The P&T Committee will meet quarterly to review new and existing drugs and/or drug classes and recommend pharmaceutical agents for inclusion or exclusion on the UF based on their relative clinical and cost effectiveness.

D. Formulary Resources for Beneficiaries – The TRICARE Pharmacy website (www.tricare.osd.mil/pharmacy) was recently restructured to provide additional information to DoD beneficiaries regarding the pharmacy benefit. The site now provides general formulary information, information about eligibility and claims, MTF and retail pharmacy locators, and a Formulary Search Tool.

The Formulary Search Tool enables beneficiaries to determine cost share, availability, prior authorization status, and quantity limits for specific medications at retail network pharmacies and the mail order pharmacy. A particular strength is the fact that the database searched by the tool is not limited to medications available through the pharmacy benefit, allowing a beneficiary to determine, for example, that a particular medication is over-the-counter, not covered by TRICARE, or covered by TRICARE but not considered to be part of the pharmacy benefit. The Formulary Search Tool also designates whether medications are listed on the BCF and provides information on whether generic equivalents are available for specific medications.

E. High Dollar Drugs – The introduction of clinically effective but costly new therapies can have a large, unexpected, negative impact on MTF pharmacy budgets. To complicate the issue, many of these new agents are biotech agents administered in inpatient or office/clinic settings, and therefore covered under the TRICARE medical benefit rather than the pharmacy benefit. Unfortunately, there is no uniform mechanism or policy in place across the services, or even across MTFs within a service, for dealing with this type of budget impact. Shifting use of the product to the network to be covered under the medical benefit will minimize pharmacy budget impact but increase the cost to the facility, since it will be billed for the network care. The P&T Committee concluded that attention needs to be given to formulating a uniform policy for handling high cost medications within the direct care system.

Col Nancy Misel, BSC, USAF, Director of the Air Force High Dollar Drug Program, briefed the P&T Committee on the program used by the Air Force to address this issue. Initiated at Wright-Patterson AFB in 1995, the High Dollar program is a centrally funded air staff program that provides high cost medications, on an individual patient basis, to

Air Force MTFs at no cost to the MTF. The criteria for drugs to be included in the program are predominantly based on cost. Other factors that would place a drug within the scope of the program include drugs with restricted distribution requirements that require administrative actions to procure or dispense (e.g., thalidomide) and drugs with low use and/or narrow therapeutic ranges. The program permits facilities to appropriately manage patient care without cost shifting to another venue or adversely impacting the local budget. It also ensures that funds for these medications do not need to be distributed to multiple locations and that access to medications is not interrupted when patients relocate or deploy.

Approximately 100 medications are being supplied under the current program guidelines, with approximately 75% of those drugs being new to the market since program implementation. The estimated expenditure for FY 05 is $25M. Advantages of the centralized program include 100% inventory control, minimization of MTF inventory requirements, the ability for a MTF to return unused drugs for future use at another MTF, expenditures which are easily attributable to user facilities, and a source for clinical oversight and support, as MTF expertise with these drugs may be limited. In addition, the program utilizes TRICARE quantity limits and prior authorization criteria to ensure an even playing field with the retail network and TRICARE Mail Order Pharmacy (TMOP) Program.

Col Misel noted that the Air Force program could be either the core for an expanded centrally-funded program, or easily exported to the other services, and is one option for dealing with the impact of costly therapies in the direct care system.

6. DRUG REVIEW PROCESS

Under 10 U.S.C. § 1074g and 32 C.F.R. 199.21, the DoD P&T Committee is responsible for developing the UF. Recommendations to the Director, TMA, on formulary status, preauthorizations, and the effective date for a drug's change from formulary to non-formulary status must be reviewed by the Beneficiary Advisory Panel (BAP) before the Director may make a final decision. Additionally, the P&T Committee may make recommendations on quantity limits, medical necessity criteria for non-formulary pharmaceutical agents, and additions, deletions, or clarifications to drugs that are on the BCF and ECF. These recommendations do not require review and comment by the BAP prior to decision by the Director. Finally, there are certain administrative processes required for the day-to-day operation of the UF that do not require recommendations or action by the P&T Committee or final decision by the Director, TMA, before they can be implemented. The P&T Committee developed a comprehensive list of functions associated with formulary management and categorized each in one of these three decision process categories which are outlined in Table 1.

Table 1: Processes and Recommendation/Approval Authorities

Process	Function
Administrative (not part of DoD P&T Committee process, Beneficiary Advisory Panel (BAP) comments not required, Director, TMA, approval not required) Responsible parties include: TRICARE Mail Order Pharmacy and TRICARE Retail Pharmacy Contracting Officer Representatives (TMOP and TRRx CORs), TMA Pharmacy Program, TMA Office of General Counsel, and Pharmacoeconomic Center (PEC) staff	▪ Identification of new FDA-approved medications, formulations, strengths, package sizes, etc. ▪ If situation unclear, determination as to whether a new FDA-approved medication is covered by TRICARE ▪ If situation unclear, determination as to whether a new FDA-approved medication is part of the pharmacy benefit ▪ If situation unclear, determination as to whether a new FDA-approved medication is suitable for dispensing through the TRICARE Mail Order Pharmacy (TMOP) ▪ Calculating and implementing quantity limits if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making changes to quantity limits as needed based on non-clinical factors such as changes to packaging (e.g., medication previously available in boxes of 5 now only available packaged in boxes of 8) ▪ Establishing adjudication edits (PDTS limitations which are set well above the clinical maximum and are intended to prevent entry errors [e.g., entering a quantity of 17 for a 17-gram inhaler for which the actual unit of measure is 1 inhaler] or are intended to limit diversion) ▪ Implementing prior authorization requirements if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making minor changes to prior authorization forms NOT involving changes to underlying criteria, such as correcting contact information or rewording clinical questions ▪ Making changes to PA criteria, medical necessity criteria, quantity limits and any associated documents to accommodate new FDA-approved indications or respond to changes in FDA-recommended safety limitations (changes will be reviewed by DoD P&T Committee at next meeting) ▪ Removing medications withdrawn from the U.S. market from Basic Core Formulary (BCF) or Extended Core Formulary (ECF) listings and other documents ▪ Providing clarifications to existing listings on the BCF or ECF to specify specific brands/manufacturers when a joint DoD/VA mandatory source generic contract is awarded for a given product (i.e., clarifying an existing listing for “atenolol” to include the contractual requirement to use a specific manufacturer’s products) ▪ As necessary to accomplish functions above: for example, making changes to PDTS coding for TMOP & TRRx, communicating status of medications as part of the pharmacy or medical benefit to Managed Care Support Contractors (MCSCs), making changes to the TMA Pharmacy website and the TRICARE Formulary Search Tool, and making changes to BCF and ECF listings on the PEC website.
Approval by Director, TMA, required based on DoD P&T Committee recommendations and BAP comments	▪ Classification of a medication as non-formulary on the Uniform Formulary (UF), and implementation plan (including effective date) ▪ Establishment of prior authorization requirement for a medication or class of medications, summary/outline of prior authorization criteria, and implementation plan (including effective date) ▪ Changes to existing prior authorization and medical necessity criteria (e.g., due to the availability of new efficacy or safety data) ▪ Discontinuation of prior authorization requirements
Approval by Director, TMA, required based on DoD P&T Committee recommendations (not required to be submitted to BAP for comments)	▪ Establishment of quantity limits for a medication or class of medications; deletion of existing quantity limits; changes to existing quantity limits based on clinical factors (e.g., new clinical data or dosing regimens) ▪ Establishment of medical necessity criteria for non-formulary agents ▪ Addition, deletion of medications listed on the Basic Core Formulary (BCF) or Extended Core Formulary (ECF)

7. PRIOR AUTHORIZATIONS

The P&T Committee reviewed existing prior authorizations and recommended rules that can be applied immediately to drugs approved by the Food and Drug Administration (FDA) between Committee meetings, when the drug belongs to a drug class for which prior

authorizations already exist. The recommended rules would provide a consistent benefit and avoid circumstances under which a newly approved medication, very similar to another medication for which a prior authorization exists, is on the UF for several months of unrestricted use before a prior authorization can be applied. The PEC would report changes to prior authorizations following these general rules at the next scheduled DoD P&T Committee meeting.

COMMITTEE ACTION: The P&T Committee made the following recommendations regarding rules that can be applied immediately to drugs approved by the FDA between P&T Committee meetings:

- *Phosphodiesterase-5* (*PDE-5) inhibitors* – Any new PDE-5 inhibitor that may become available for the treatment of erectile dysfunction will be subject to the same prior authorization as the existing agents – 14 for, 0 opposed, 1 abstention, 3 absent.
- *Injectable gonadotropins* – Any new injectable gonadotropin that may become available for infertility treatment will be subject to the same prior authorization as the existing agents – 15 for, 0 opposed, 1 abstention, 2 absent.
- *Antifungals for onychomycosis* - Any new oral or topical antifungal that may become available for the treatment of onychomycosis will be subject to the same prior authorization as the existing agents, with course of therapy limits set based on recommended dosing – 15 for, 0 opposed, 1 abstain, 2 absent.
- *Growth hormone agents* - Any new growth hormone agent that may become available will be subject to the same prior authorization as the existing agents – 15 for, 0 opposed, 1 abstention, 2 absent.

8. REVIEW OF QUANTITY LIMITS

The P&T Committee reviewed all current quantity limits with two goals: 1) to recommend any necessary additions, deletions, or changes; and 2) to formulate and recommend rules for those quantity limits that apply to groups of medications (e.g., oral inhalers, “triptans,” PDE-5 inhibitors), including new medications or formulations as soon as they become available.

The quantity limits rules formulated by the P&T Committee for groups of medications include a number of factors which must be considered: the maximum quantity typically required by patients (usually based on product labeling); FDA-recommended safety recommendations in product labeling or other safety concerns; commercial package sizes available, and whether a given package size is typically dispensed to patients as a unit; and the operational requirement that 90-day limits should be three times the 30-day limits whenever possible. It should be noted that quantity limits have several operational safeguards in place to accommodate individual patient needs, including an exception process for patients with a valid clinical need for greater quantities than provided for by the quantity limits, and provisions to allow for dose changes, vacation supplies, and deployment supplies.

The P&T Committee noted that quantity limits apply to MTFs, as well as to the TMOP, and the retail pharmacy network. Network retail pharmacies typically dispense up to a 30-day supply of medications, although patients may obtain up to a 90-day supply of most medications by paying the appropriate multiple cost shares. The TMOP dispenses up to a 90-day supply. MTFs make local decisions as to days supply dispensed, but typically dispense a 90-day supply of chronic medications. Accordingly, quantity limits are listed in these

minutes as amounts per 30 or 90 days whenever possible. It is anticipated that MTFs will most often utilize the quantity limits that apply to the TMOP.

A. Quantity Limit Rules: The P&T Committee recommended the establishment of quantity limit rules that apply to groups of medications, including new medications or formulations as soon as they become available. This will provide a consistent benefit and avoid circumstances under which quantity limits exist for very similar medications, but which are applied to newly-approved medications of the same type only after several months of unrestricted use. The PEC would report changes in quantity limits following these general rules at the next scheduled DoD P&T Committee meeting.

COMMITTEE ACTION: The P&T Committee recommended the establishment of quantity limit rules for the following groups of medications. Details may be found in Appendix A.

- Medications for the treatment of erectile dysfunction (PDE-5 inhibitors and injectable/intraurethral prostaglandins) – 16 for, 1 opposed, 1 abstention
- 5-hydroxytryptamine (serotonin) receptor 3 (5-HT3) antagonists (antiemetic medications) – 17 for, 0 opposed, 1 abstention
- 5-hydroxytryptamine-1 (5HT-1) receptor agonists ("triptans") for the treatment of migraine- 17 for, 0 opposed, 1 abstention
- Dihydroergotamine products for the treatment of migraine – 17 for, 0 opposed, 1 abstention
- Fertility agents (injectable gonadotropins) – 17 for, 0 opposed, 1 abstention
- Nasal inhalers for the treatment of allergic and nonallergic rhinitis – 17 for, 0 opposed, 1 abstention
- Oral inhalers and inhalant solutions for the treatment of asthma, chronic obstructive lung disease, or allergies – 17 for, 0 opposed, 1 abstention
- Tramadol-containing products – 17 for, 0 opposed, 1 abstention

B. Quantity Limit Changes: The P&T Committee recommended specific changes to QLs for one product.

COMMITTEE ACTION: The P&T Committee recommended a reduction in QLs for this product. Details may be found in Appendix A.

- Dihydroergotamine nasal spray (Migranal) – change to 16 amps per 30 days; 48 amps per 90 days – 17 for, 0 opposed, 1 abstention

C. Quantity Limit Establishment: The P&T Committee recommended establishment of QLs for several drugs.

COMMITTEE ACTION: The P&T Committee recommended establishment of QLs for two drugs, both of which are very similar to medications which already have QLs. Details may be found in Appendix A.

- Azelastine nasal spray (Astelin) – 1 bottle per 30 days or 3 bottles per 90 days – 17 for, 0 opposed, 1 abstention
- Tazarotene (Tazorac) cream – 60 gm (1 large tube) per 30 days; 180 gm per 90 days – 17 for, 0 opposed, 1 abstention

D. Quantity Limit Deletion: The P&T Committee recommended deletion of QLs for several drugs.

COMMITTEE ACTION: The P&T Committee recommended deletion of QLs for five drugs. Details may be found in Appendix A.

- Azithromycin (Zithromax) 250- and 600-mg tablets – 17 for, 0 opposed, 1 abstention
- Dornase alpha inhalation solution (Pulmozyme) – 17 for, 0 opposed, 1 abstention
- Fluconazole (Diflucan, generics) 150 mg tablets – 17 for, 0 opposed, 1 abstention
- Imiquimod cream (Aldara) – 13 for, 4 opposed, 1 abstention
- Testosterone buccal system (Striant) – 17 for, 0 opposed, 1 abstention

9. REVIEW OF RECENTLY-APPROVED AGENTS

The PEC presented clinical information on 13 new medications approved by the FDA and introduced to the U.S. market since the July 2004 meeting (see Appendix A). Since none of the new medications fall into drug classes already reviewed by the P&T Committee, UF consideration was deferred until drug class reviews are completed. The P&T Committee did not recommend prior authorization requirements for any of the new drugs.

The PEC also informed the P&T Committee of two newly approved medications that do not fall under the outpatient pharmacy benefit, but may substantially impact MTF pharmacy budgets. These medications are natalizumab (Tysabri), an intravenous infusion for the treatment of multiple sclerosis, and pegaptanib (Macugen), an intravitreous injection for the treatment of neovascular (wet) age-related macular degeneration. [Note: as of February 28, 2005, distribution of natalizumab was suspended by the manufacturer due to two serious adverse events, including one fatal case and one possible case of progressive multifocal leukoencephalopathy.]

COMMITTEE ACTION

The P&T Committee recommended quantity limits for the following recently approved products:

- Erlotinib tabs (Tarceva) – limit of 30 day supply in retail, 45 day supply in TMOP, up to 45 day supply in MTFs. No multiple fills for multiple cost shares in retail and TMOP – 16 for, 0 opposed, 1 abstention, 1 absent at time of vote.
- Gemifloxacin tablets (Factive) – limit of 7 days supply per 30 days in retail, TMOP, and MTFs - 16 for, 0 opposed, 1 abstention, 1 absent at time of vote.

10. BASIC CORE FORMULARY (BCF) ISSUES

The BCF is a subset of the UF and is a mandatory component of all MTF pharmacy formularies. The DoD P&T Committee previously placed timolol maleate ophthalmic solution and gel on the BCF. Timolol maleate ophthalmic solution 0.25% and 0.5%, administered twice daily, are available with a contract price of $1.52 per 5 ml. Timolol maleate ophthalmic gel 0.25% and 0.5%, administered once daily, are available at the contract price of $10.57 and $12.81 per 5 ml for the 0.25% and 0.5%, respectively.

Timolol maleate 0.5% ophthalmic solution (Istalol) was approved by the FDA in June 2004, and became available on the market in January 2005. Istalol contains potassium sorbate, which is stated to enhance the bioavailability of the drug in solution, allowing for once daily administration. Istalol has similar efficacy, safety, and tolerability compared to timolol maleate products currently on the BCF, but costs much more, with a FSS price of $24.33 per 5 ml. The FDA has given Istalol a Therapeutic Equivalent Code of BT, meaning that it is a topical product that has acceptable clinical performance, but is not bioequivalent to other pharmaceutically equivalent products or lacks sufficient evidence of bioequivalence.

MTFs are advised that the BCF listing for timolol maleate products relates to the product for which DoD has a sole source contract, and does not include the Istalol brand of timolol maleate ophthalmic solution.

11. ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) DRUG CLASS REVIEW

A. ARB Uniform Formulary Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the seven ARBs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcome. The ARB therapeutic class was defined as losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the Uniform Formulary unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

There has been an increase in the use of ARBs over the past five years, and the class is now in the top 10 of MHS drug class expenditures. The P&T Committee agreed that in the MHS, ARBs are not recommended as first-line agents for treating hypertension due to their higher cost and fewer trials supporting a mortality reduction, compared to diuretics or angiotensin converting enzyme (ACE) inhibitors. The ACE inhibitors and ARBs have similar safety concerns regarding hyperkalemia, elevations of serum creatinine, angioedema, and pregnancy category labeling. The ARBs have an incidence of cough similar to placebo. An ARB is an appropriate agent for hypertension if a patient cannot tolerate an ACE inhibitor.

1.) Efficacy for Hypertension: All seven ARBs are approved by the FDA for treating hypertension. In clinical trials, ARBs lowered systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure by 4.5 to 6.5 mm Hg, compared to placebo. The P&T Committee agreed that there is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

2). Efficacy for Chronic Heart Failure: When evaluating the ARBs for treatment of chronic heart failure, the P&T Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as hospitalization for heart failure or death) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in pulmonary capillary wedge pressure).

Two ARBs have clinical evidence from large, well-conducted, randomized controlled trials showing a reduction in the risk of hospitalization due to chronic heart failure, a clinically relevant outcome. Based on the results of the Val-HeFT trial, the FDA approved valsartan for use in patients with heart failure who are intolerant of ACE inhibitors. The CHARM trials with candesartan support its use in chronic heart failure, although at the time of the meeting the FDA had not yet approved candesartan for this indication. (Note: Candesartan was approved for heart failure on February

22, 2005, following the DoD P&T committee meeting). The P&T Committee agreed that there was no evidence that either valsartan or candesartan were preferable relative to the other for the treatment of chronic heart failure. Since none of the other ARBs have outcome studies showing a reduction in clinically relevant outcomes related to chronic heart failure, the P&T Committee agreed that valsartan and candesartan were preferable to the other five ARBs for the treatment of heart failure.

3.) *Efficacy for Type 2 Diabetic Nephropathy*: When evaluating the ARBs for treatment of type 2 diabetics with nephropathy, the P&T Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as development of end stage renal disease, the need for dialysis or renal transplantation, or death) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in the urinary albumin to creatinine ratio, urinary albumin excretion rate, or glomerular filtration rate).

Based on the results of the RENAAL and IDNT trials, the FDA has approved two ARBs, losartan and irbesartan, respectively, for treatment of diabetics who have an elevated serum creatinine and proteinuria. The P&T Committee agreed that there was no evidence that either losartan or irbesartan were preferable relative to the other for the treatment of renal nephropathy in type 2 diabetics. Since none of the other ARBs have outcome studies showing a reduction in clinically relevant outcomes related to Type 2 diabetic nephropathy, the P&T Committee agreed that losartan and irbesartan were preferable to the other five ARBs for the treatment of Type 2 diabetic nephropathy.

4.) *Safety/Tolerability:* The P&T Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability. These medications are generally well-tolerated, with adverse event rates for all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum creatinine, and angioedema, do not appear to differ among agents. Drug interaction profiles are similar. All ARBs are pregnancy category C during the first trimester, and pregnancy category D during the second and third trimesters, based on the occurrence of fetal abnormalities with ACE inhibitors.

Conclusion: The P&T Committee concluded that (1) all seven ARBs have similar relative clinical effectiveness for treating hypertension; (2) that candesartan and valsartan have similar relative clinical effectiveness for treating chronic heart failure; (3) that losartan and irbesartan have similar relative clinical effectiveness for treating Type 2 diabetics with nephropathy; and (4) that all seven ARBs have similar safety and tolerability profiles. Valsartan, candesartan, losartan, and irbesartan have higher clinical utility (overall clinical usefulness) relative to the three ARBs that are indicated solely for treating hypertension (telmisartan, eprosartan, and olmesartan).

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstention) to accept the conclusion that valsartan, candesartan, losartan, and irbesartan have increased clinical utility (due to their evidence for uses in addition to hypertension) relative to the three ARBs that are only indicated for treating hypertension (telmisartan, olmesartan, and eprosartan), and concluded that there is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

B. ARB Uniform Formulary Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost-effectiveness of the agents within the ARB therapeutic class, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). The preceding conclusion from the P&T Committee that all seven ARBs showed similar relative clinical effectiveness for treating hypertension; that candesartan and valsartan showed similar relative clinical effectiveness for treating chronic heart failure, and that losartan and irbesartan showed similar relative clinical effectiveness for treating Type 2 diabetic nephropathy was incorporated into the models. Given the results of the clinical analysis, a series of cost-minimization analyses (CMA) were conducted which revealed: that: candesartan was more cost-effective relative to valsartan for the treatment of heart failure; irbesartan was more cost-effective relative to losartan for treatment of Type 2 diabetic nephropathy; and irbesartan was more cost-effective relative to the other ARBs for the treatment of hypertension. Moreover, it was determined that eprosartan was not cost-effective relative to the other hypertension-only ARBs (telmisartan and olmesartan).

The results of the CMA were subsequently incorporated into a BIA, which accounts for other factors and costs associated with a potential decision to recommend one or more ARBs status be changed from formulary to non-formulary such as: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and costs incurred while switching patients from non-formulary agents to formulary agents. The results of the budget impact analyses further confirmed the results from the cost minimization analyses. Eprosartan was found not to be cost-effective relative to the other hypertension ARBs.

Conclusion: The P&T Committee concluded that eprosartan was not cost-effective relative to the other ARBs for treating hypertension. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee recommended that eprosartan's status be changed from formulary to non-formulary, with candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan maintaining formulary status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (9 for, 7 opposed, 1 abstention, 1 absent) to recommend formulary status for candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, and non-formulary status for eprosartan under the UF.

C. ARB Uniform Formulary Medical Necessity Criteria: Based on the clinical evaluation of eprosartan and the conditions for establishing medical necessity for a non-formulary medication provided for in the Uniform Formulary rule, the following medical necessity criteria were proposed for eprosartan.

1.) Use of all the formulary ARBs (losartan, irbesartan, valsartan, candesartan, telmisartan, and olmesartan), is contraindicated, and the use of eprosartan is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from all the formulary ARBs (losartan, irbesartan, valsartan, candesartan, telmisartan, and olmesartan) and the patient is reasonably expected to tolerate eprosartan.

3.) Use of the formulary ARBs (losartan, irbesartan, valsartan, candesartan, telmisartan, and olmesartan) resulted in therapeutic failure, and the patient is reasonably expected to respond to eprosartan.

4.) The patient has previously responded to eprosartan, and changing to a formulary ARB would incur unacceptable risk.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstention, 2 absent) to recommend the medical necessity criteria for eprosartan listed above.

D. ARB Uniform Formulary Implementation Plan: Because relatively few patients are receiving eprosartan at any MHS pharmacy point of service (less than 1% of all patients receiving ARBs), the P&T Committee proposed a 30-day transition period for implementation of a decision by the Director, TMA, to classify eprosartan as non-formulary on the UF. Prior to the P&T Committee meeting, the Government had solicited a request for blanket purchase agreement (BPA) price quotes from manufacturers. One manufacturer subsequently filed a protest concerning this class with the Government Accountability Office (GAO). Any decision by the Director, TMA, concerning this class, including an implementation plan, may proceed; however, no award of a BPA, based on these quotes will occur until after the GAO has issued a ruling on the protest. The TMA and PEC web sites will notify all interested parties when GAO has ruled on the protest, and what subsequent decisions have been made.

MTFs are not allowed to have non-formulary pharmaceutical agents on their local formularies. MTFs will be able to fill non-formulary requests for non-formulary agents only if both of the following conditions are met: 1) the prescription is written by a MTF provider, and 2) the beneficiary and/or his or her provider has established medical necessity for the agent. MTFs may (but are not required to) fill a non-formulary prescription written by a non-MTF provider to whom the patient was referred as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstention, 2 absent) to recommend an effective date of 30 days from the final decision date if the Director, TMA, approves the P&T Committee's recommendation.

E. ARB Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the ARBs recommended for inclusion on the UF to select a BCF ARB. It had previously been decided that at least one, but no more than three ARBs, could be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Within the MTFs, the majority of ARB usage is for treating hypertension, and not for treating chronic heart failure or Type 2 diabetic nephropathy. Although valsartan, candesartan, irbesartan, and losartan have additional indications, which are of importance in the UF at the MTF setting, selecting one BCF ARB with a sole indication for hypertension is sufficient to meet the needs of the majority of patients. The relative clinical effectiveness review demonstrated that all seven ARBs have similar efficacy, safety, and tolerability for treating hypertension. The six remaining UF ARBs were reviewed for placement on the BCF for the treatment of hypertension. The same process used for the UF relative cost-effectiveness decision, i.e., a cost-minimization analysis

(CMA) followed by a budget impact analysis (BIA), was employed for the BCF decision. The CMA revealed, and the BIA confirmed, that telmisartan was the most cost-effective ARB for the MTF point of service. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing telmisartan on the BCF. MTFs can add additional ARBs to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place telmisartan as the sole ARB on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, none opposed, 2 abstentions, 1 absent) to recommend telmisartan as the BCF agent.

12. PROTON PUMP INHIBITORS (PPIs) DRUG CLASS REVIEW

A. PPI Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved proton pump inhibitors available in the U.S. The PPI therapeutic class was defined as omeprazole (Prilosec, Zegerid & generics), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix) and esomeprazole (Nexium). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

PPIs are among the top 10 MHS drug class expenditures. The P&T Committee agreed that in the MHS, PPIs are not recommended as first-line agents for treating gastroesophageal reflux disease (GERD), and they are not intended for the immediate relief of infrequent GERD symptoms. For GERD symptom relief, PPIs are best used after lifestyle modification, antacid, and histamine-2 (H2) blocker therapies have failed. PPIs are first-line therapy for peptic ulcer disease (PUD), whether non-steroidal anti-inflammatory drug (NSAID)-induced, associated with *Helicobacter pylori* infection, or due to a hypersecretory condition.

1.) Efficacy: Although FDA indications differ slightly amongst the PPIs, the vast majority of studies found no significant difference in efficacy in treating GERD and PUD. Minor differences in clinical utility, such as pediatric indication, possible need for dosage adjustment in hepatic failure, and availability of alternative dosage forms were noted. After a review of head-to-head trials and meta-analyses, the P&T Committee concluded that all of the PPIs show similar efficacy when equivalent doses are used.

2.) Safety/Tolerability: The P&T Committee found that PPIs were not significantly different with respect to major contraindications, drug interactions, and adverse drug events. The dropout rates in clinical trials due to adverse events were comparable amongst the five PPIs. All PPIs are pregnancy category B, except omeprazole, which is category C.

Conclusion: The P&T Committee concluded that all PPIs have similar relative clinical effectiveness for treating GERD and PUD. All five PPIs have similar safety and tolerability profiles.

COMMITTEE ACTION*:* The P&T Committee, based upon its collective professional judgment, concluded that all five PPIs demonstrate similar relative clinical effectiveness. (16 for, 0 opposed, 1 abstained, 1 absent).

B. PPI Uniform Formulary Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Two analyses were used to determine the relative cost-effectiveness of agents within the PPI therapeutic class; a pharmacoeconomic analysis using cost-minimization techniques, and a budget impact analysis (BIA). Cost-minimization (CMA) was chosen for the pharmacoeconomic analysis because the clinical analysis, determined the outcomes of interest (effectiveness, safety, and tolerability) to be similar among all the PPIs.

Results of the CMA showed omeprazole to be the most cost-effective PPI across all points of service (MTF, Retail, Mail), followed by rabeprazole, lansoprazole, and pantoprazole. It was determined that esomeprazole was not cost effective relative to the other PPIs

The results of the CMA were then incorporated into a BIA, which accounts for other factors and costs associated with a potential decision regarding formulary status of PPIs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA. Esomeprazole was found not to be cost effective relative to the other PPIs.

Conclusion: The P&T Committee concluded that esomeprazole was not cost effective relative to the other PPIs. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs and other relevant factors, the P&T Committee recommended that esomeprazole's status be changed from formulary to non-formulary, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status with the formulary cost share, and omeprazole maintaining formulary status with a generic cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 2 opposed, 1 abstained, 1 absent) to recommend non-formulary status for esomeprazole, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status at the formulary cost share, and omeprazole maintaining formulary status at the generic cost share.

C. PPI Uniform Formulary Medical Necessity Criteria: Based on the clinical evaluation of esomeprazole, and the conditions for establishing medical necessity for a non-formulary medication provided for in the Uniform Formulary rule, the P&T Committee recommended the following medical necessity criteria for esomeprazole.

1.) Use of all formulary PPIs (omeprazole, rabeprazole, lansoprazole, and pantoprazole) is contraindicated, and the use of esomeprazole is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from all the formulary PPIs (omeprazole, rabeprazole, lansoprazole, and pantoprazole), and the patient is reasonably expected to tolerate esomeprazole.

3.) Use of the formulary PPIs (omeprazole, rabeprazole, lansoprazole, and pantoprazole) resulted in therapeutic failure, and the patient is reasonably expected to respond to esomeprazole.

4.) The patient has previously responded to the non-formulary esomeprazole, and changing to a formulary PPIs (omeprazole, rabeprazole, lansoprazole, and pantoprazole) would incur unacceptable risk.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstention, 1 absent) to approve the medical necessity criteria.

D. PPI Uniform Formulary Implementation Plan: Because a substantial number of patients are currently receiving esomeprazole from one of the three MHS pharmacy points of service (138,739 patients, 13.4 % of all patients receiving PPIs) the P&T Committee proposed a 90-day transition period for implementation of the decision to change esomeprazole to a non-formulary drug on the UF. Patients wishing to fill prescriptions for esomeprazole at retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for esomeprazole is established by the beneficiary and/or his or her provider.

Prior to the implementation of the UF, the former DoD P&T Committee had made a decision that prescriptions for esomeprazole could not be filled through the TMOP, unless medical necessity was validated. If the Director, TMA, concurs in the P&T Committee's recommendation, prescriptions for esomeprazole may be filled through the TMOP, but will require payment of the non-formulary cost share of $22. Beneficiaries who already have a medical necessity validation on file at the TMOP are required to re-establish medical necessity for esomeprazole under the medical necessity criteria approved by the Director, TMA, in order to receive esomeprazole at the formulary cost share.

MTFs will not be allowed to have esomeprazole on their local formularies. MTFs will be able to fill non-formulary requests for esomeprazole only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary and/or his or her provider must establish medical necessity for esomeprazole. MTFs may (but are not required to) fill an esomeprazole prescription written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstention, 1 absent) to recommend an effective date of 90 days from the final decision date (the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the P&T Committee's recommendation).

***E. PPI BCF Review and Recommendations*:** The P&T Committee reviewed the PPIs recommended for inclusion on the UF to select a BCF PPI. It had previously been decided that at least one but no more than two PPIs could be added to the BCF, based on the outcome of the relative clinical effectiveness and relative cost effectiveness determinations.

The same process for the UF decision was used for the BCF decision, which consisted of evaluating the relative cost-effectiveness with a cost-minimization analysis (CMA),

followed by a budget impact analysis (BIA). The CMA revealed, and the BIA confirmed, that omeprazole (generic) and rabeprazole (Aciphex) were the most cost-effective PPIs for the MTF point of service. Based on the relative clinical and cost-effectiveness, the P&T Committee recommended placing omeprazole (generic) and rabeprazole (Aciphex) on the BCF. However, omeprazole suspension (Zegerid) and Prilosec 40 mg were not included on the BCF, because they were less cost-effective than the generic omeprazole.

Conclusion: Omeprazole and rabeprazole were recommended for inclusion on the BCF. Omeprazole suspension (Zegerid) and Prilosec 40 mg were not included on the BCF, because they were less cost-effective than the generic omeprazole.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to recommend that omeprazole and rabeprazole be on the BCF.

14. ADJOURNMENT

The second day of the meeting adjourned at 1730 hours on February 16, 2005. The dates of the next meeting are May 16–19, 2005.

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Patricia L. Buss
CAPT, MC, USN
Chairperson

List of Appendices

Appendix A: Recommended Changes to Quantity Limits

Medications	Committee Recommendation	Comments
General Quantity Limit Rules		
Medications for the treatment of erectile dysfunction (ED) Phosphodiesterase-5 (PDE-5) inhibitors [sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)] Injectable / intraurethral prostaglandins [alprostadil] injection (Caverject, Edex); alprostadil intraurethral pellet (Muse)]	Quantity limits will apply to all injectable/intraurethral prostaglandins and PDE-5 inhibitors for the treatment of ED, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits will be based on the following: 6 tablets, injections, or intraurethral pellets per 30-day supply or 18 per 90-day supply, consistent with current quantity limits for PDE-5 inhibitors and injectable/intraurethral prostaglandins. This quantity limit will apply collectively to all strengths and formulations of all injectable/intraurethral prostaglandins and PDE-5 inhibitors for the treatment of ED.	The rule would represent a change from quantity limits currently in place for the PDE-5 inhibitors and the injectable / intraurethral prostaglandins (as listed on the TMA Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#ED) in that it provides for a collective quantity limit for this entire group of medications. Currently, collective quantity limits are in place for PDE-5 inhibitors and for injectable / intraurethral prostaglandins, but they do not apply across the entire group of medications.
5-HT3 receptor antagonists (antiemetic medications) Dolasetron (Anzemet) Granisetron (Kytril) Ondansetron (Zofran)].	Quantity limits will apply to all 5-HT3 receptor antagonists, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: quantities sufficient to allow for chemotherapy prophylaxis and post-operative use based on recommended dosing regimens, taking into account FDA safety recommendations in product labeling and other safety concerns; commercial package sizes; and operational requirements.	Quantity limits are currently in place for the three available 5-HT3 receptor antagonists, as listed on the TMA Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Antiemetics.
5HT-1 receptor agonists ("triptans) for the treatment of migraine Almotriptan (Axert) Eletriptan (Relpax) Frovatriptan (Frova) Naratriptan (Amerge) Rizatriptan (Maxalt) Sumatriptan (Imitrex) Zolmitriptan (Zomig)	Quantity limits will apply to all 5HT1 receptor agonists ("triptans") for the treatment of migraine, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: sufficient quantities to allow for recommended dosing regimens for the treatment of migraine, not to exceed the treatment of an average of more than 4 migraine attacks in a 30-day period based on FDA safety recommendations in product labeling; other safety concerns; commercial package sizes; and operational requirements.	Quantity limits are currently in place for the seven available 5HT-1 receptor agonists ("triptans") for the treatment of migraine, as listed on the TMA Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Antimigraine.

Medications	Committee Recommendation	Comments
Dihydroergotamine products for the treatment of migraine Dihydroergotamine nasal spray (Migranal) Dihydroergotamine injection (DHE-45, generics)	Quantity limits will apply to all dihydroergotamine products for the treatment of migraine, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: sufficient quantities to allow for recommended dosing regimens for the treatment of migraine, not to exceed more than 4 mg of the nasal spray or more than 6 mL of the injectable product per week, based on FDA safety recommendations in product labeling; other safety concerns; commercial package sizes; and operational requirements.	Quantity limits are currently in place for these medications, as listed on the TRICARE Management Activity Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Antimigraine.
Fertility agents (injectable gonadotropins) Follitropin alpha Follitropin beta Menotropins Urofollitropin	Quantity limits will apply for all injectable gonadotropins for the treatment of infertility, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits will be based on the following: 3600 IU (or equivalent) per 30 day supply, no refills, in all pharmacy points of service, consistent with current quantity limits for injectable prostaglandins. This quantity limit will apply collectively to all injectable gonadotropins (no more than 3600 IU of any combination of products per 30 days in any pharmacy point of service, no refills).	This would represent a change from quantity limits currently in place for the injectable gonadotropins (as listed on the TMA Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Fertility) in that it provides for a collective quantity limit for this group of medications. Currently, quantity limits are in place for injectable gonadotropins but they do not apply across the entire class of medications. A collective quantity limit is desirable to prevent patients from accumulating excessive quantities of injectable gonadotropins by submitting prescriptions for two or more different injectable gonadotropins during the same time period.
Nasal inhalers for the treatment of allergic and nonallergic rhinitis Multiple products, including nasal corticosteroids, ipratropium, and antihistamines	Quantity limits will apply to all nasal inhalers for the treatment of allergic and nonallergic rhinitis, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: sufficient quantities to allow for recommended dosing regimens for the treatment of allergic and nonallergic rhinitis, taking into account FDA safety recommendations in product labeling, and other safety concerns; commercial package sizes; and operational requirements.	Quantity limits are currently in place for the medications in this category, as listed on the TRICARE Management Activity Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Nasal.

Medications	Committee Recommendation	Comments
Oral inhalers and inhalant solutions for the treatment of asthma, chronic obstructive lung disease, or allergies Multiple products, including oral inhaled corticosteroids, bronchodilators, mast cell stabilizers, and combination products	Quantity limits will apply to all oral inhalers and inhalant solutions for the treatment of asthma, chronic obstructive lung disease, or allergies, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: sufficient quantities to allow for recommended dosing regimens, taking into account FDA safety recommendations in product labeling and other safety concerns; sufficient quantities to allow for an extra inhaler at school or place of business for those inhalers (multi-dose inhalers or dry powder inhalers) commonly given as needed for acute treatment of bronchospasm; commercial package sizes; and operational requirements.	Quantity limits are currently in place for the medications in this category, as listed on the TRICARE Management Activity Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Oral. The rule would represent a change from current quantity limits by allowing an extra inhaler for "rescue" medications for acute treatment of bronchospasm (e.g., albuterol).
Tramadol-containing products Tramadol (Ultram, generics) Tramadol/acetaminophen (Ultracet)	Quantity limits will apply to tramadol-containing products, including new FDA-approved medications and new formulations of existing medications as soon as they become available, and will be adjusted as necessary to accommodate changes in recommended dosing regimens and commercial package sizes available. Quantity limits for these medications will be set based on the following factors: sufficient quantities to allow for recommended dosing regimens, taking into account FDA safety recommendations in product labeling and other safety concerns; commercial package sizes; and operational requirements. These quantity limits would apply collectively to all tramadol-containing products, unless a newly approved product required a more stringent limitation for safety reasons.	A collective quantity limit is currently in place for tramadol (Ultram, generics) and tramadol / acetaminophen (Ultracet) (as listed on the TRICARE Management Activity Pharmacy website at www.tricare.osd.mil/pharmacy/quant_limits.cfm#Miscellaneous), based on FDA safety recommendations in product labeling (maximum of no more than 8 tablets per 24 hour period).
Specific Changes to Quantity Limits		
Dihydroergotamine nasal spray (Migranal)	Change in quantity limits to 16 amps per 30 days; 48 amps per 90 days	Dihydroergotamine nasal spray (Migranal) is used for the treatment of migraine. It comes in a kit with 4 ampules. Each 1 mL ampule contains 4 mg. A dose is 2 (0.5 mg per spray, 1 mg total). The weekly max per FDA safety recommendations is 4 mg; however, a patient may use up to 3 mg in a 24 hour period. A patient may potentially use as many as 4 ampules per week if he or she only uses one dose per ampule. The P&T Committee agreed that the current quantity limits for this medications (30 amps per 30 days; 90 amps per 90 days) are too high, and recommended changing them to 16 amps per 30 days; 48 amps per 90 days.

Medications	Committee Recommendation	Comments
Azelastine nasal spray (Astelin)	Establishment of quantity limits: 1 bottle per 30 days or 3 bottles per 90 days	Azelastine (Astelin) is an antihistamine indicated for the treatment of seasonal allergic rhinitis and vasomotor rhinitis. It is packaged in bottles containing approximately 200 sprays (about 1 months supply). Based on the precedent for quantity limits for other nasal inhalers for the treatment of allergic and nonallergic rhinitis, the P&T Committee recommended a quantity limit of 1 bottle per 30 days; 3 bottles per 90 days.
Tazarotene 0.05% and 0.1% cream (Tazorac)	Establishment of quantity limits: 60 gm (1 large tube) per 30 days or 180 gm (3 large tubes) per 90 days	Currently, quantity limits exist for tazarotene (Tazorac) gel, but not for tazarotene (Tazorac) cream. Both formulations are used for the treatment of acne and psoriasis. The P&T Committee agreed that tazarotene (Tazorac) cream should have a quantity limit consistent with that currently in place for tazarotene gel, which equates to 1 large tube per 30 days, 3 large tubes per 90 days. The P&T Committee noted that tazarotene cream is also available by the brand name Avage, which is not a covered benefit under TRICARE, since the sole FDA-approved indication is for wrinkling, hypopigmentation, and lentigines (age spots).
Azithromycin (Zithromax) 250- and 600-mg tablets	Deletion of quantity limits	The P&T Committee agreed that while azithromycin 250 mg is a costly, widely used antibiotic that has a high potential for inappropriate use, most of that inappropriate use is for the treatment of viral infections. The existence of a quantity limit is unlikely to influence such use. The P&T Committee also did not see the need for a quantity limit for the 600-mg strength of azithromycin, which is less commonly used and unlikely to be inappropriately prescribed, particularly since the quantity limit currently in place is not adequate for the treatment of disseminated Mycobacterium avium complex (MAC) disease.
Dornase alpha inhalation solution (Pulmozyme)	Deletion of quantity limit	This product is given by nebulization once to twice daily for the treatment of cystic fibrosis. Based on previous DoD P&T Committee minutes, the current quantity limits were set to allow for an alternative dosing regimen (4 ampules twice daily, two weeks on, two weeks off). It is not clear that this regimen is currently in clinical use. Since the quantity limits are probably set too high to influence use and since the potential for inappropriate use is unclear for this specialized indication, the P&T Committee recommended deleting the quantity limit for dornase alpha.

Medications	Committee Recommendation	Comments
Fluconazole (Diflucan, generics) 150 mg tablets	Deletion of quantity limit	Historically, the 150 mg tablet of fluconazole was far more costly than other strengths since it was intended and specially packaged for single-dose use for the treatment of vaginal candidiasis. Since fluconazole is available as 50-, 100-, and 200-mg tablets, there was no justification for using the 150-mg tablets for other indications, which typically require daily dosing. Fluconazole 150 mg tablets are now generically available and available at a much lower cost ($6.63 per tablet in 2001 for brand name Diflucan vs. $0.18 in Feb 05 for the generic equivalent, based on FSS prices). Although there is still little reason to use the 150 mg strength of fluconazole for other indications, the P&T Committee agreed that the cost differential between the strengths no longer warrants the existence of a specific quantity limit.
Imiquimod cream (Aldara)	Deletion of quantity limit	Imiquimod has a long-standing FDA indication for genital/perianal warts (3 times per week for maximum of 16 weeks) and two new indications, for actinic keratoses (2 times per week for 16 weeks) and superficial basal cell carcinoma (5 times per week for 6 weeks). Labeling for superficial basal cell carcinoma recommends dispensing no more than 3 boxes (36 individual packets) per 6-week treatment period. The current quantity limit for imiquimod is for 12 packets per 30 days or 36 packets per 90 days, which is not adequate for superficial basal cell carcinoma based on approved dosing. Imiquimod is a costly medication and the potential for wastage appears relatively high. Given the new indication, however, the P&T Committee recommended deleting the quantity limit for imiquimod. They requested that the PEC monitor imiquimod utilization for excessive use.
Testosterone buccal system (Striant)	Deletion of quantity limit	This product is the only testosterone replacement product for which a specific quantity limit is listed. This dosage form does not appear to be any more likely to be used inappropriately than other testosterone replacement products.

Appendix B – Newly Approved Drugs

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Acamprosate (Campral) tabs; Forest; glutamate receptor modulator (alcohol deterrent)	Jul 04: Maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with Campral should be part of a comprehensive management program that includes psychosocial support.	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Apomorphine (Apokyn) SQ injection; Bertek ; dopamine agonist	April 04: Acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's Disease. Has been studied as an adjunct to other medications. Note: Not available at TMOP due to controlled distribution requirements.	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Duloxetine (Cymbalta) capsules; Eli Lilly; serotonin norepinephrine reuptake inhibitor (SNRI)	Aug 04: Treatment of major depressive disorder (MDD). Also indicated for management of neuropathic pain associated with diabetic peripheral neuropathy.	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Erlotinib (Tarceva) tabs; Genentech / OSI; human epidermal growth factor receptor type 1 (HER1/EGFR1) tyrosine kinase inhibitor	Nov 04: Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.	Quantity limits recommended due to precedent set by the other HER1/EGFR1, gefitinib (Iressa); potential for wastage; and high cost: Limit of 30 day supply in retail, 45 day supply in TMOP, up to 45 day supply in MTFs. No multiple fills for multiple cost shares in retail and TMOP. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Ezetimibe / simvastatin (Vytorin) tabs; Merck Schering Plough; cholesterol absorption inhibitor plus statin	Aug 04: Primary Hypercholesterolemia: Indicated as adjunctive therapy to diet for the reduction of elevated total-C. LDL-C, Apo B, TG and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia. Homozygous Familial Hypercholesterolemia: Indicated for the reduction in elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Gemifloxacin (Factive) tabs; Oscient; fluoroquinolone antibiotic	April 03: Community-acquired pneumonia (includes multi-drug resistant strains of *Strep. pneumoniae);* and acute exacerbations of chronic bronchitis	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed. Quantity limits recommended based on the maximum 7-day course of therapy and FDA safety recommendations noting a much higher incidence of rash—which can be severe—if treated for more than 10 days. The product is packaged only in 5s and 7s. Recommendation: Limit of 7 days supply (one course of therapy) per 30 days in retail, TMOP, and MTFs.
Lanthanum carbonate (Fosrenol) chewable tabs; Shire Phosphate binder (rare earth metal; trivalent cation)	Oct 04: Indicated to reduce serum phosphate in patients with End Stage Renal Disease (ESRD)	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Overactive Bladder Medications		
Darifenacin (Enablex) sustained release tabs; Novartis; muscarinic antagonist	Dec 04: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Solifenacin (Vesicare) tabs; GSK/Yamanouchi; muscarinic antagonist	Nov 04: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	
Trospium (Sanctura) tabs; Indevus; muscarinic antagonist	May 04: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	
Rifaximin (Xifaxan) tabs; Salix; rifampin derivative antibiotic (nonabsorbed)	May 04: Treatment of patients $\geq$12 years of age with traveler's diarrhea caused by non-invasive strains of *Escherichia coli.* Rifaximin should not be used in patients where *Campylobacter jejuni, Shigella* spp, or S*almonella* spp are suspected as causative pathogens. Rifaximin should not be used for diarrhea complicated by fever of bloody stools. (Orphan status for hepatic encephalopathy)	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Telithromycin (Ketek) tabs; Sanofi-Aventis; ketolide / macrolide antibiotic	April 04: Treatment of patients 18 years and older with the following conditions: community-acquired pneumonia due to *Streptococcus pneumoniae* (includes multi-drug resistant isolates [MDRSP]), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae*, or *Mycoplasma pneumoniea***;** acute exacerbations of chronic bronchitis (AECB) due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis***;** sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis* or *Staphylococcus aureus.*	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.
Tinidazole (Tindamax) tabs; Presutti Labs; anti-protozoal antibiotic	May 04: Treatment of trichomoniasis in post-pubertal female and male patients caused by *T. vaginalis*; giardiasis caused by *G. duodenalis* (also termed *G. lamblia*) in both adults and pediatric patients**;** intestinal amebiasis (amebic dysentery) and amebic liver abscess caused by *E. histolytica* in both adults and pediatric patients older than 3 years of age.	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until drug class is reviewed.

14 July 2004

DECISION PAPER:
JULY 2004 PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

7. BASIC CORE FORMULARY (BCF) CHANGES

A. Estrogen Replacement Therapy Patches (Esclim):

The Committee recommended removing Esclim from the BCF because the price increased from $5.20 per cycle to $27.50 per cycle. (See paragraph 7. A. on page 4 of P&T Committee minutes)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

The Committee recommended changing the BCF listing to "estradiol patch" with no specific brand listed. (See paragraph 7. A. on page 4 of P&T Committee minutes)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

B. Ciprofloxacin (Cipro, generics):

The Committee recommended adding ciprofloxacin to the BCF because it is a cost-effective alternative to other fluoroquinolones for treating susceptible infections. (See paragraph 7. B. on pages 4 and 5 of P&T Committee minutes)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

C. Lamivudine/Zidovudine (Combivir):

The Committee recommended not adding Combivir to the BCF. (See paragraph 7. C. on page 5 of P&T Committee minutes)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

D. Erythromycin/Sulfisoxazole (Pediazole):

The Committee recommended removing erythromycin ethylsuccinate / sulfisoxazole from the BCF due to increasing microbial resistance, the absence of erythromycin ethylsuccinate / sulfisoxazole from current guidelines for acute otitis media, and low utilization at MTFs. (See paragraph 7. D. on page 5 of the P&T Committee minutes).

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

E. Ramipril (Altace):

The Committee recommended removing ramipril from the BCF because it is now significantly less cost effective than the other ACE inhibitors on the BCF. (See paragraph 7. E. on page 5 of the P&T Committee minutes)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

12. PRIOR AUTHORIZATIONS

A. ***COMMITTEE ACTION****:* The Committee recommended retaining existing prior authorizations criteria for the following drugs (See paragraph 12. A. on page 7 of P&T Committee minutes and Appendix A for the rationale):

- Adalimumab (Humira®)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Anakinra (Kineret®)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Efalizumab (Raptiva®)

TMA Director Decision: ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Ciclopirox (Penlac)

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Itraconazole (Sporanox)

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Terbinafine (Lamisil)

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Human growth hormone (somatropin, somatrem)

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

- Injectable gonadotropins

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

B. ***COMMITTEE ACTION****:* The Committee recommended continuation of the requirement for prior authorization of etanercept (Enbrel), with the addition of a criterion that covers the new FDA-approved indication for the treatment of adult patients (≥18 years of age) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (See paragraph 12. A. on page 7 and Appendix A of P&T Committee minutes for rationale)

*TMA Director Decision***:** ■ Approved □ Disapproved
□ Approved, but modified as follows:

C. ***COMMITTEE ACTION:*** The Committee recommended continuation of prior authorization of PDE-5 inhibitors, but with modifications designed to improve the efficiency of the prior authorization process. Contingent upon the ASD(HA) rescinding HA Policy 98-040, Practice Guidelines for the Evaluation of Patients Requesting Sildenafil (Viagra) for the Treatment of Male Impotence, the Committee recommended:

- Allowing male patients 50 years of age or older to receive PDE-5 inhibitors without going through the PA process, and
- Eliminating the drug interaction with nitrates from the PA criteria.

Note: The cumulative quantity limit of 6 tablets per 30 days in the retail network or 18 tablets per 90 days in the TMOP remain in effect. (See paragraph 12 B. on page 8 and Appendix A of P&T Committee minutes for rationale)

*TMA Director Decision***:** ■ Approved □ Disapproved

□ Approved, but modified as follows:

DECISION ON RECOMMENDATIONS

TMA Director decisions are as annotated above.

William Winkenwerder, Jr., M.D.
Date:
OCT 5 2004

Department of Defense
Pharmacy and Therapeutics Committee Minutes

14 July 2004

1. CONVENING

The DoD P&T Committee convened at 0800 hours on 13 and 14 July 2004 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CAPT Patricia Buss, MC	DoD P& T Committee Chair
COL Daniel Remund, MS	DoD P& T Committee Recorder
Col James Young, BSC (Representing COL William Davies)	Deputy Director, DoD Pharmacy Programs, TMA (Representing Director, DoD Pharmacy Programs, TMA)
Lt Col Gordon Wright Bates, Jr., MC	Air Force, OB/GYN Physician
Maj Nick Conger, MC	Air Force, Physician at Large
Col Phil Samples, BSC	Air Force, Pharmacy Officer
CDR William Hall, MC	Navy, Internal Medicine Physician
LCDR Suzanne Haney, MC (via VTC)	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
LT Joseph Lawrence, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Franklin H. Hauger, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
COL Kent Maneval, MS (Representing MAJ Travis Watson, MS)	Joint Readiness Clinical Advisory Board (Representing Army, Pharmacy Officer)
CDR Patrick Marshall	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC	Contracting Officer Representative, TRRx
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

COL Greg Wickern, MC (deployed)	Air Force, Internal Medicine Physician

NON-VOTING MEMBERS PRESENT

Howard Altschwager	Deputy General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
MAJ John Howe, MS	Defense Supply Center Philadelphia

NON-VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
CDR Mary Fong	Coast Guard, Pharmacy Officer Alternate
COL Mike Heath, MS, USA (Via VTC July 13th only)	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
CAPT Betsy Nolan, MSC (Via VTC July 13th only)	Navy Pharmacy Specialty Leader
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC	DoD Pharmacoeconomic Center
CAPT Don Nichols, MC	DoD Pharmacoeconomic Center
Lt Col Dave Bennett, BSC	DoD Pharmacoeconomic Center
Lt Col Barb Roach, MC	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Janet Daily	Department of Veterans Affairs
Paul Vasquez	Defense Supply Center Philadelphia
Lynn Burleson	Assistant General Counsel, TMA
CDR Mark Richerson, MSC	Future PEC Director

3. REVIEW MINUTES OF LAST MEETING

This is the first meeting of the restructured DoD Pharmacy and Therapeutics (P&T) Committee under the new charter established under the authority of 10 U.S.C. 1074g and 32 C.F.R. 199.21. The P&T Committee approved the minutes of the last meeting of the previous Committee with a correction to page 7 Section 6A of the Executive Council minutes regarding prices for salmeterol and formoterol: Based on current FSS prices and recommended dosing regimens, salmeterol costs $44.57 per month compared to $32.63 per month for formoterol.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

None.

5. ORIENTATION/EDUCATION OF THE DOD P&T COMMITTEE

TMA and PEC staff members briefed the Committee on the following:

- Overview of the DoD pharmacy benefit
- Overview of the Uniform Formulary and Basic Core Formulary
- DoD P&T Committee processes under the new charter
- Beneficiary Advisory Panel
- Ethical issues
- Drug class review process
- New drug review process

TMA, PEC, and DSC-P staff are working to revise certain provisions in existing pharmaceutical contracts are in conflict with provisions of the 32 C.F.R 199.21. Additionally, procedures are being developed for DoD to receive price information from pharmaceutical companies for consideration in Uniform Formulary decisions.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAS)

A. *New Contracts Awarded* – midazolam HCL 1 mg/mL and 5 mg/mL.

B. *Changes to Existing Contracts*—The next option year was exercised for contracts on the following drugs: ticlopidine, naproxen, propofol, ethinyl estradiol 35 mcg/ethynodiol diacetate 1 mg, ethinyl estradiol 35 mcg/norethindrone 1 mg, norethindrone 35 mcg, ondansetron, digoxin, simvastatin, acyclovir, valproic acid, nicotine patches, glyburide, benztropine, fluphenazine, chlorhexidine, indomethacin, ketoconazole cream, adsorbase ointment, paclitaxel, carbidopa/levodopa, and zolmitriptan.

C. *Contracts Pending Award* – amantadine, enalapril, salsalate, fluocinonide topical, nortriptyline, verapamil SA and insulin.

D. The Committee reviewed utilization and cost data for drug classes where national contracts or blanket purchase agreements currently exist: statins, triptans, fluoroquinolones, leutinizing hormone releasing hormone (LHRH) agonists, ophthalmic prostaglandins, thiazolidinediones (TZDs) and 2nd generation antihistamines. More information about DoD and DoD/VA national pharmaceutical contracts may be found on the Defense Supply Center Philadelphia (DSCP) DMM-Online website at http://dmmonline.dscp.dla.mil/pharm/contractlist.asp. Contract guidance for the oral fluoroquinolones, statins, leutinizing hormone releasing hormone (LHRH) agonists, and triptans are available on the PEC website at www.pec.ha.osd.mil/national_contracts.htm.

7. BASIC CORE FORMULARY (BCF) CHANGES AND CLARIFICATIONS

The committee voted (17 for, 0 opposed, 1 abstained) to require that any requests for BCF additions or deletions from individual providers must be approved by and forwarded through the MTF Pharmacy and Therapeutics Committee before being considered by this committee.

A. *Estrogen Replacement Therapy Patches (Esclim):* Esclim was added to the BCF in May 2003 on the basis of a BPA price of $5.20 per cycle (8 patches = 28 days supply) for all

strengths. Women's First Healthcare, the U.S. distributor of Esclim, filed for Chapter 11 reorganization on May 29, 2004. The FSS contract for Esclim was terminated subsequent to the filing for reorganization. The absence of the FSS contract has caused Esclim's price to increase to $27.50 per month, a 5-fold increase. Women's First Healthcare is in the process of selling their marketing rights to Esclim, but it will likely be one to three months before another FSS contract is in place. Prices for estradiol patches are displayed in Table 1 below.

Table 1. July 2004 FSS Prices per Cycle for Estradiol Patches

Brand	Manufacturer	Dosing Schedule	0.025 mg	0.0375 mg	0.05 mg	0.06 mg	0.075 mg	0.1 mg
Esclim	WFH	Twice weekly	$26.60 (formerly $5.20)	$26.86 (formerly $5.20)	$27.38 (formerly $5.20)		$27.89 (formerly $5.20)	$27.89 (formerly $5.20)
Estraderm	Novartis	Twice weekly			$17.94			$19.36
Climara	Berlex	Once weekly	$7.74	$17.85	$7.74	$18.45	$7.74	$7.74
Vivelle	Novartis	Twice weekly	$19.04	$19.59	$20.86		$20.76	$21.74
Vivelle Dot	Novartis	Twice weekly	$18.07	$16.35	$17.42		$17.21	$18.37
Alora	Watson	Twice weekly	$19.04		$18.22		$21.85	$18.89
Generic	Mylan	Once weekly			$11.18			$11.65

COMMITTEE ACTION: The Committee recommended (17 for, 0 opposed, 1 abstained) to remove Esclim from the BCF and change the BCF listing to "estradiol patch" with no specific brand listed. MTFs can decide if they want to switch to a different estradiol patch or continue to use Esclim with the anticipation that the price of Esclim will be reduced in the near future. The DoD P&T Committee will reconsider the class for BCF and/or Uniform Formulary selections once the pricing issue has resolved.

B. *Ciprofloxacin (Cipro, generics):* Ciprofloxacin prices have decreased significantly due to the availability of generic equivalents for Cipro. As shown in Table 2, ciprofloxacin now costs much less than other fluoroquinolones.

Table 2. July 2004 MTF Fluoroquinolone Prices

Gatifloxacin	Moxifloxacin	Levofloxacin	Ciprofloxacin (Bayer)*	Ciprofloxacin (PAR)	Ciprofloxacin (Ivax)
$1.35/tab (all strengths)	$1.55/tablet (all strengths)	$4.39/250 mg $5.06/500 mg $5.50/750 mg	$0.19/tab (all strengths) $0.40/tab XR	$0.28/250 mg $0.34/500 mg $0.40/750 mg	$0.06/250 mg $0.095/500 mg $0.12/750 mg

*NOTE: Bayer's Cipro prices are only available through direct purchase, not from Prime Vendors (PVs). Prices for Cipro similar to the direct prices from Bayer will be available at PVs in the near future**.** Ciprofloxacin (PAR) prices are based on commercial pricing. Ciprofloxacin (Ivax) are July 2004 FSS prices. Prices for gatifloxacin, moxifloxacin and levofloxacin are based on the most current contract, incentive agreement, and FSS prices, respectively, effective as of July 2004.

Ciprofloxacin lacks good gram-positive coverage, so gatifloxacin is still the preferred fluoroquinolone for the treatment of community acquired pneumonia (CAP) and sinusitis. The gatifloxacin contract allows ciprofloxacin to be on formularies for the treatment of conditions other than CAP or sinusitis. Ciprofloxacin is a cost effective alternative to other fluoroquinolones for treating susceptible infections.

***COMMITTEE ACTION**:* The Committee recommended (17 for, 0 opposed, 1 abstained) addition of ciprofloxacin to the BCF, because it is a cost-effective alternative to other fluoroquinolones for treating susceptible infections.

C. *Lamivudine/Zidovudine (Combivir)*: An MTF provider requested the addition of Combivir (300mg zidovudine plus 150mg lamivudine given BID) to the BCF for HIV post-exposure prophylaxis (PEP). There is currently no medication on the BCF to fulfill the OSHA requirement for PEP. U.S. Public Health Service guidelines for PEP are available on the CDC website at www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm. Lamivudine and zidovudine are identified in the U.S. Public Health Service guidelines as an option for initial PEP prophylaxis. Some committee members expressed the opinion that this issue was already covered by the OSHA requirement and that medications for PEP prophylaxis should not be specified on the BCF, because they are not a primary care issue.

***COMMITTEE ACTION**:* The Committee recommended (15 for, 1 opposed, 1 abstained, 1 absent from the room) to not add Combivir to the BCF. The Committee reminds MTFs of the requirement to have medications for PEP readily available for their facility healthcare workers in the event of blood borne exposure.

D. *Erythromycin/Sulfisoxazole (Pediazole):* An MTF provider requested removal of erythromycin ethylsuccinate / sulfisoxazole oral suspension (Pediazole) from the BCF. Erythromycin ethylsuccinate / sulfisoxazole is indicated for the treatment of acute otitis media caused by susceptible strains of *Haemophilus influenzae* in children.

The May 2004 guideline from the Subcommittee on Management of Acute Otitis Media (sponsored by the American Academy of Pediatrics and the American Academy of Family Physicians) does not include erythromycin ethylsuccinate / sulfisoxazole. MTF utilization of erythromycin ethylsuccinate / sulfisoxazole is extremely low, about 400 prescriptions per month. Provider responses support the removal of erythromycin ethylsuccinate / sulfisoxazole from the BCF.

***COMMITTEE ACTION**:* The Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent from the room) to remove erythromycin ethylsuccinate / sulfisoxazole from the BCF, due to increasing microbial resistance, absence of erythromycin ethylsuccinate / sulfisoxazole from current guidelines for acute otitis media, and low utilization at MTFs.

E. *Ramipril (Altace):* Ramipril (Altace) has been priced at $0.12 per capsule for the past few years under a voluntary price reduction from Monarch. Monarch recently renegotiated the FSS price for ramipril and discontinued the voluntary price reduction. The FSS price for ramipril is now $0.52-$0.65 / capsule. The two other ACE inhibitors on the BCF are lisinopril ($0.04 to $0.18 per dose) and captopril ($0.01 to $0.05 per dose).

***COMMITTEE ACTION**:* The Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent from the room) to remove ramipril from the BCF because it is now significantly less cost effective than the other ACE inhibitors on the BCF.

8. ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

Merck submitted a "pre-award" GAO protest of the blanket purchase agreement (BPA) request for price quotes that the Defense Supply Center Philadelphia (DSCP) issued to companies that market ARBs. DSCP decided to cancel the BPA request for price quotes. The Committee intends to evaluate the relative clinical effectiveness and relative cost effectiveness of the ARBs to make recommendations for the Uniform Formulary and BCF at a future meeting.

9. PROTON PUMP INHIBITORS (PPIs)

The Committee reviewed clinical information, and concluded that one or more proton pump inhibitors (PPIs) could potentially be classified as non-formulary on the Uniform Formulary if there are differences in the relative cost effectiveness of the PPIs. The committee intends to evaluate the relative clinical effectiveness and relative cost effectiveness of the PPIs to make recommendations for the Uniform Formulary and BCF at a future meeting.

10. NEW DRUGS

A. *Cinacalcet tablets (Sensipar)* were approved by the FDA in March 2004. Cinacalcet is a calcimimetic and is approved for treating secondary hyperparathyroidism (PTH) in dialysis patients with chronic kidney disease. It is also designated as an orphan drug for treating hypercalcemia associated with parathyroid carcinoma. Cinacalcet increases sensitivity of the calcium-sensing receptor on the PTH gland to extracellular calcium, directly reducing PTH levels, and accordingly reducing serum calcium levels. Serum concentrations of ionized PTH, calcium, phosphorus, and calcium/phosphorus double product normalized in 40% of dialysis patients receiving cinacalcet vs. 5% with placebo ($p = 0.001$). Patients must be monitored for development of hypocalcemia and resultant increased seizure risk.

   COMMITTEE ACTION: The Committee voted (17 for, 0 opposed, 1 abstained) to add cinacalcet to the TMOP formulary without requirements for prior authorization or quantity limits, but not to add it to the BCF.

B. *Sertaconazole 2% cream (Ertaczo)* is a topical antifungal of the azole class, similar to clotrimazole and miconazole. Sertaconazole was approved in December 2003 for treating interdigital tinea pedis in immunocompetent patients older than 12 years of age. Other topical antifungals have additional indications to include tinea cruris, tinea corporis, cutaneous candidiasis, and tinea versicolor. The two clinical trials used for FDA approval compared sertaconazole with a vehicle control, and showed significant improvements in complete cure rates (13.1% vs. 3.3% in study one and 27.3% vs. 4.9% in study two).

   COMMITTEE ACTION: The Committee voted (17 for, 0 opposed, 1 abstained) to add sertaconazole to the TMOP formulary without requirements for prior authorization or quantity limits, but not to add it to the BCF. Since 13 topical antifungals are available in the U.S., the Committee intends to evaluate topical antifungals to make recommendations for the Uniform Formulary and BCF at a future meeting.

11. ENFUVIRTIDE (FUZEON) INJECTION

Enfuvirtide (Fuzeon) is an injectable medication indicated in combination with other antiretroviral agents to treat HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The injections are given subcutaneously twice daily and may be self-administered, although the first injection should be performed under the supervision of a qualified healthcare provider. As of April 26, 2004, enfuvirtide was removed from the restricted distribution program that had previously precluded it from being dispensed by the TMOP.

COMMITTEE ACTION*:* The Committee voted (16 for, 1 opposed, 1 abstained) to add enfuvirtide to the TMOP Covered Injectables List with quantity limit of 1 kit (30-days supply) in the retail network and 2 kits (60-day supply) in the TMOP. The quantity limits are intended to minimize potential wastage of a medication that has a current FSS price of $1,259.38/kit.

12. PRIOR AUTHORIZATIONS

A. *Current Prior Authorizations*: Prior authorizations (PAs) are currently performed in the TMOP and TRRx network pharmacies for:

- Phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil)
- Biologic agents for rheumatoid arthritis, psoriasis, or related conditions (etanercept, adalimumab, anakinra, efalizumab)
- Antifungals for onychomycosis (ciclopirox topical solution, itraconazole capsules, terbinafine tablets)
- Fertility agents (injectable gonadotropins)
  - Human growth hormone (somatropin, somatrem)

The Committee reviewed the background, rationale, and criteria for the prior authorizations, which are provided in Appendix A.

COMMITTEE ACTION*:* The Committee chose to make no recommendation (16 for, 0 opposed, 1 abstained, 1 absent from the room) to change prior authorizations with the existing criteria for the following:

- Adalimumab (Humira®)
- Anakinra (Kineret®)
- Efalizumab (Raptiva®)
  - Antifungals for onychomycosis
  - Growth hormone
  - Injectable gonadotropins

COMMITTEE ACTION*:* The Committee chose to make no recommendation (16 for, 0 against, 1 abstained, 1 absent from the room) to change the prior authorization of etanercept, except for adding an additional criterion that covers a new FDA-approved indication for the treatment of adult patients (≥18 years of age) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The Committee decided not to include an age limitation in the PA criteria for etanercept since the medication has clinical trial evidence supporting safety in pediatric patients and an

FDA-approved indication in this age group (for juvenile rheumatoid arthritis). The previous criteria and the revised criteria are included in Appendix A.

B. *PDE-5 Inhibitor PA*: Health Affairs Policy 98-040, Practice Guidelines for the Evaluation of Patients Requesting Sildenafil (Viagra) for the Treatment of Male Impotence, which applies to all PDE-5 inhibitors, imposes prior authorization criteria on PDE-5 inhibitors. TRICARE covers the treatment of erectile dysfunction of organic etiology but not erectile dysfunction that is solely due to psychogenic causes. The PA for PDE-5 inhibitors is primarily based on this coverage issue. As males age, erectile dysfunction is increasingly likely to be at least partially due to organic causes. The efficiency of the PA for PDE-5 inhibitors could be improved by targeting the prior authorization process at the subset of patients who are most likely to have erectile dysfunction of psychogenic etiology (i.e., patients under the age of 50). The existing PDE-5 inhibitor PA criteria also deny coverage to patients who are also receiving nitrates, a well-known, potentially severe drug interaction. The Committee noted that since the policy was first issued, the Pharmacy Data Transaction Service (PDTS) now provides real-time, point-of-care alerts concerning drug interactions between PDE-5 inhibitors and nitrates, therefore, it would not be necessary to include this drug interaction in the PA criteria.

COMMITTEE ACTION: The Committee agreed to have the Chair of the Committee prepare a recommendation to the ASD(HA) to modify or rescind the policy and approve a prior authorization recommended by the Committee instead. If the ASD(HA) concurs in the recommendation to modify or rescind the Health Affairs Policy, the Committee recommended (16 for, 0 against, 1 abstained, 1 absent from the room) to continue prior authorization of PDE-5 inhibitors with modifications designed to improve the efficiency of the prior authorization process:

- Allowing male patients 50 years of age or older to receive PDE-5 inhibitors without going through the PA process, and
- Eliminating the drug interaction with nitrates from the PA criteria.

Since at least 85% of patients obtaining PDE-5 inhibitors through the retail network or mail order are ≥ 50 years of age, this would greatly decrease the administrative costs of performing the PA, while reducing the paperwork required on the part of beneficiaries and providers. The established quantity limits would continue to apply (no more than 6 per 30 days of any combination of PDE-5 inhibitors at retail network pharmacies or 18 per 90 days of any combination of PDE-5 inhibitors at mail order).

13. QUANTITY LIMITS

A. *Etanercept Quantity Limits*: The FDA approval of etanercept for the treatment of psoriasis necessitates a change in the quantity limits, because the recommended adult dosing of etanercept for psoriasis is higher than for other indications for the first 3 months of therapy.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 abstained, 1 absent from the room) to set the etanercept quantity limit at a six-week supply in mail order and a four-week supply in retail network pharmacies, with the number of vials dispensed based on the instructions for use on the prescription. The maximum days supply

dispensed at any one time in retail network pharmacies would continue to be limited to four weeks.

B. *Current Quantity Limits*: The Committee reviewed the existing quantity limits.

COMMITTEE ACTION: The Committee reviewed the quantity limits currently in place and voted (16 for, 0 opposed, 1 abstained, 1 absent from the room) that they be continued without change. The Committee members plan to review the list of quantity limits in greater detail and will bring comments to a future meeting. A list of quantity limits is available in Appendix B.

14. ADJOURNMENT

The meeting adjourned at 1730 hours. The date of the next meeting has not been determined.

Patricia Buss

PATRICIA L. BUSS
CAPT, MC, USN
Chair

List of Appendices

Appendix A – Prior Authorization Criteria in the TRICARE Mail Order Pharmacy and TRICARE Retail Pharmacy Programs

Background

Prior authorizations (PAs) have been a part of the mail order program since 1999. In the retail network, Managed Care Support Contractors (MCSCs) have generally used the same PAs and criteria approved by the DoD P&T Committee for the TMOP. Under 32 CFR 199.21(k), prior authorizations now apply across all points of service. PA Forms and criteria may be found at: www.pec.ha.osd.mil/PA_Criteria_and_forms.htm

Prior Authorization Medications

Phosphodiesterase-5 (PDE-5) Inhibitors – sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®)

A PA and quantity limit for sildenafil was put into place in mail order in Aug 1999, based on Health Affairs Policy 98-040, Practice Guidelines for the Evaluation of Patients Requesting Sildenafil (Viagra™) for the Treatment of Male Impotence, released 6 Aug 1998. Vardenafil was included in the PA program in Nov 2003 and tadalafil in Feb 2004. TMA has determined that provisions of the sildenafil policy apply to these new PDE-5 inhibitors.

Among other provisions, the policy requires that

- PDE-5 inhibitors will not be a formulary item for Military Treatment Facilities (MTFs), National Mail Order Pharmacy (NMOP, the previous mail order program), and for Managed Care Support Contractor retail networks (now the TRICARE Retail Pharmacy program).
- Physicians treating patients with erectile dysfunction may special order PDE-5 inhibitors when the results of their evaluation indicate the medication as the most optimal regimen for the patient. MTFs will not fill special orders from non-network civilian providers unless there is proof of compliance with the prescribing guidance contained in the Health Affairs Policy 98-040.
- Only 6 tablets may be dispensed per month. "Lost", "stolen", or "destroyed" tablets will not be replaced. Prescriptions filled through Standard CHAMPUS will be reimbursed for only 6 tablets per month and must be accompanied by proof of compliance with clinical guidelines.

The accompanying prescribing guidelines include establishing that the erectile dysfunction is organic in origin.

The PDE-5 inhibitors are currently non-formulary at TMOP, but available if PA criteria are met. The quantity limit of 6 per 30 days has been implemented across the class – that is, a patient may obtain only 6 tablets of any combination of these medications per 30 days in the retail network, and only 18 tablets of any combination of these medications per 90 days in mail order.

Existing PA Criteria for PDE-5 Inhibitors for the Treatment of Erectile Dysfunction

- Coverage not provided for female sexual dysfunction, males under 18 years of age, patients receiving any form of nitrate therapy, or psychogenic erectile dysfunction.
- Coverage provided for organic erectile dysfunction, erectile dysfunction with an organic component, or drug-induced erectile dysfunction where the causative drug cannot be altered or discontinued. Approval is good for 12 months.
- *Note:* PDE-5 inhibitors are subject to a cumulative quantity limit of 6 tablets per 30 days in the retail network or 18 tablets per 90 days in the TMOP.

Revised PA Criteria for PDE-5 Inhibitors for the Treatment of Erectile Dysfunction if the ASD(HA) concurs in the modification or rescission of HA Policy 98-040

- Coverage not provided for female sexual dysfunction, males under 18 years of age, or psychogenic erectile dysfunction.
- Coverage provided for organic erectile dysfunction, erectile dysfunction with an organic component, or drug-induced erectile dysfunction where the causative drug cannot be altered or discontinued. Approval is good for 12 months.
- *Note:* Prior authorization is required for coverage of PDE-5 inhibitors for erectile dysfunction for male patients 18 to 49 years of age. Prior authorization is not required for male patients 50 years of age and older.
- *Note:* PDE-5 inhibitors are subject to a cumulative quantity limit of 6 tablets per 30 days in the retail network or 18 tablets per 90 days in the TMOP.

Etanercept (Enbrel®)

The PA for etanercept was approved by the DoD P&T Committee in May 1999 and implemented in Aug 1999. The rationale for the PA was high cost and potential for inappropriate use.

A quantity limit of 8 vials (a 4-week supply) was initially set for the mail order program, then changed to a 6-week supply (12 vials) in Aug 1999 to allow time for refills to be ordered and received by patients. A quantity limit of 8 vials (a four-week supply) was established in retail.

Existing PA Criteria for Etanercept

- Coverage provided for the treatment of
    - Moderately to severely active rheumatoid arthritis
    - Active psoriatic arthritis
    - Active ankylosing spondylitis
    - Juvenile rheumatoid arthritis when the patient has an inadequate response to at least one disease-modifying antirheumatic drug (DMARD).
- Coverage NOT provided for concomitant use with adalimumab (Humira), anakinra (Kineret), or infliximab (Remicade).
- *Note:* Etanercept is subject to a quantity limit of 8 vials (four-week supply) in retail and 12 vials (six-week supply) in mail order.

Note: Criteria for etanercept and the other biologics have primarily been based on the FDA indications, which closely follow the available clinical evidence for these medications.

Revised PA Criteria for Etanercept

- Coverage provided for the treatment of:
    - Moderately to severely active rheumatoid arthritis
    - Active psoriatic arthritis
    - Active ankylosing spondylitis
    - Juvenile rheumatoid arthritis when the patient has an inadequate response to at least one DMARD
    - Chronic moderate to severe plaque psoriasis when the patient has tried and failed traditional therapy, such as phototherapy (e.g., UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR is not a candidate for phototherapy or systemic therapy
- Coverage NOT provided for concomitant use with adalimumab (Humira), anakinra (Kineret), or infliximab (Remicade).
- *Note:* Etanercept is subject to a quantity limit of a four-week supply in retail and a six-week supply in mail order (based on instructions for use on the prescription).

Adalimumab (Humira®)

A PA for adalimumab was implemented in mail order in March 2003. The rationale for the PA was high cost, potential for inappropriate use, and the existence of a PA for similar agents.

PA Criteria for Adalimumab

- Coverage provided for the treatment of moderately to severely active rheumatoid arthritis in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD).
- Coverage NOT provided for concomitant use with anakinra (Kineret), etanercept (Enbrel), or infliximab (Remicade).
- *Note:* Adalimumab is subject to a quantity limit of a 4-week supply in retail and a 6-week supply in mail order.

Anakinra (Kineret®)

History – A PA for anakinra was implemented in mail order in Feb 2002. The rationale for the PA was high cost, potential for inappropriate use, and the existence of a PA for a similar agent.

A quantity limit of a 6-week supply (6 packages of 7 syringes) at mail order was changed to a 8-week supply (2 packages of 28 syringes) at the April 2004 DoD P&T Committee meeting because of a packaging change by the manufacturer. The quantity limit is 28 syringes (1 package) in retail.

PA Criteria for Anakinra

- Coverage provided for the treatment of moderately to severely active rheumatoid arthritis in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD).
- Coverage NOT provided for concomitant use with adalimumab (Humira), etanercept (Enbrel) or infliximab (Remicade).
- *Note:* Anakinra is subject to a quantity limit of 28 syringes (4-week supply) in retail and 56 syringes (8-week supply) in mail order.

Efalizumab (Raptiva®)

A PA for efalizumab was implemented in mail order in Feb 2004. The rationale for the PA was high cost, potential for inappropriate use, and the existence of a PA for similar agents.

PA Criteria for Efalizumab

- Coverage provided for adults (age ≥ 18 years) who meet all the following criteria:
    - Chronic moderate to severe plaque psoriasis, defined as a minimum body surface area involvement of 10% or a body surface area involvement of less than 10%, but in critical areas (e.g., palms, soles, or face) and interfering with day-to-day activities;

    AND

    - Have tried and failed traditional therapy, such as phototherapy (e.g., UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin, or cyclosporine), OR are not candidates for phototherapy or systemic therapy;

    AND

    - A dermatologist recommends treatment with efalizumab.
- Coverage NOT provided for immunocompromised patients or those receiving immunosuppressive agents, children (age < 18 years), or patients with psoriatic arthritis without plaque psoriasis.
- *Note:* No special quantity limits

Injectable gonadotropins (fertility agents)- follitropin alfa, follitropin beta, menotropins, urofollitropin (Brand names include: Gonal-F®, Follistim®, Humegon®, Pergonal®, Repronex®, Fertinex®, Bravelle®)

The Code of Federal Regulations (CFR) excludes coverage by TRICARE of services and supplies used in conjunction with noncoital reproductive technologies (e.g., *in vitro* fertilization). Compliance with the CFR in regard to fertility agents dispensed by the National Mail Order Pharmacy (NMOP) program was discussed by the DoD P&T Committee as early as Feb 1999, although at that time the NMOP contract did not provide for a prior authorization mechanism. Managed Care Support Contractors were responsible for implementing this policy in their networks, but the NMOP lacked any mechanism to ascertain whether the medications were being used for coital or noncoital reproduction. In Feb 2000, the Committee concluded that a prior authorization should be established in order to comply with TRICARE policy.

PA Criteria for Injectable Gonadotropins

- Coverage is NOT provided if the fertility agent is being prescribed for use in conjunction with a noncoital reproductive technology, including but not limited to artificial insemination, in vitro fertilization, or gamete intrafallopian transfer.
- *Note*: the PA form makes allowances for male patients being treated with injectable gonadotropins (e.g., for induction of spermatogenesis).
- *Note:* Quantity limits (3600 IU per 30 days, with no refills) are also in effect for all the injectable gonadotropins. The "no refills" provision means that patients must submit a new prescription for each cycle of therapy, although the prior authorization is good for a year.

Antifungals for onychomycosis – ciclopirox topical solution (Penlac Nail Lacquer®), terbinafine tablets (Lamisil®), and itraconazole capsules (Sporanox®)

The PA was implemented in mail order in July 2000 for terbinafine and itraconazole, with ciclopirox topical solution added in May 2001.

Rationale for PA

Because of the potential side effects, cost, and requirements for liver function testing associated with systemic antifungal therapy for onychomycosis, verifying the presence of a fungal infection prior to treatment is good clinical practice. A study published in CUTIS (1999;64:407-10) showed that as many as 35% of patients empirically diagnosed with onychomycosis did not have a fungal infection. The FDA recommends 1) definitive diagnosis of a fungal infection, 2) pretreatment lab tests, and 3) avoidance of these drugs in patients with acute or chronic liver disease. Although ciclopirox is applied topically, the prolonged course of therapy (up to 48 weeks) supports verification of an active fungal infection prior to beginning treatment.

Because it takes time for the nail to grow out following a course of systemic treatment for onychomycosis, re-treatment with systemic agents prior to 6 months is typically not necessary. *Each course of treatment with terbinafine, itraconazole, or ciclopirox for the treatment of onychomycosis requires confirmation of an active fungal infection and a separate prior authorization form.*

Criteria for Antifungals for Onychomycosis

- Coverage NOT provided for treatment of onychomycosis not confirmed by a microbiological or histological test [KOH preparation, periodic acid Schiff stain (PAS stain), or culture].
- Coverage IS provided for treatment of onychomycosis confirmed by a microbiological or histological test [KOH preparation, periodic acid Schiff stain (PAS stain), or culture].
- For terbinafine and itraconazole, coverage is approved for 6 weeks for treatment of fingernail onychomycosis and 12 weeks for treatment of toenail onychomycosis. For ciclopirox, coverage is approved for up to 48 weeks for both fingernail and toenail onychomycosis.

- Each course of treatment for onychomycosis requires confirmation of an active fungal infection and a separate prior authorization form.
- For treatment of fungal infection other than onychomycosis, coverage is approved for 12 months.
- *Note:* the PA does not apply to other formulations of ciclopirox (e.g., cream, gel, topical suspension, or shampoo) or itraconazole (e.g., injection or oral solution), since these formulations are not typically used for the treatment of onychomycosis.

Growth hormone (somatropin & somatrem)
(Brand names include: Humatrope®, Genotropin®, Norditropin®, Norditropin Depot®, Saizen®, Serostim®, Protropin®, Tev-Tropin®, Nutropin®, Nutropin AQ®, and Zorbtive®)

The DoD P&T Committee evaluated a PA for growth hormone in Feb 2004, prompted by FDA approval of a growth hormone product (Humatrope) for the treatment of non-growth hormone dependent short stature, also known as idiopathic short stature (ISS). Treatment of ISS is not considered medically necessary, and thus is not covered by TRICARE. In April 2004, the Committee approved PA criteria (developed with the assistance of a panel of MTF pediatric and adult endocrinologists) for the use of growth hormone in adults and in children. The rationale for the PA was potential for inappropriate use, TRICARE coverage rules.

A PA for growth hormone products was implemented in mail order and the retail network as of 1 June 2004, with the implementation of the TRRx program. Some or all MCSCs may already have PAs in place for growth hormone. The growth hormone PA is currently in place for new patient starts only (patients presenting a new growth hormone prescription at a retail network pharmacy or the TMOP for whom there was no prescription fill for growth hormone in the preceding 180 days). The DoD P&T Committee recommended that patients who are currently receiving growth hormone in the TMOP and retail network (based on use within the last 180 days) should be required to fulfill PA requirements within 180 days after being notified about the existence of the PA.

PA Criteria for Growth Hormone

Coverage provided for:

- Growth hormone deficiency in children and adults as a result of pituitary disease, hypothalamic disease, surgery or radiation therapy
- Chronic renal insufficiency before renal transplantation with associated short stature
- Other known renal indications: autorecessive polycystic kidney disease, cystinosis and hypophosphatemic rickets in the pediatric population
- Short stature in patients with Turner Syndrome or Prader-Willi syndrome
- Infants born small for gestational age that have not reached age appropriate height by 24 months of age
- Human immunodeficiency virus-associated wasting in adults

Coverage NOT provided for:

- Idiopathic short stature
- Depression
- Aging
- Obesity

Appendix B - Quantity Limits in the TRICARE Mail Order Pharmacy and TRICARE Retail Pharmacy Programs

The Department of Defense Pharmacy and Therapeutics (P&T) Committee has implemented quantity limits on specific medications in the TRICARE Mail Order Pharmacy (TMOP) as well as the retail network pharmacies, based on Food and Drug Administration (FDA) recommendations for dosing. Quantity limits are a common practice in commercial health plans to help ensure beneficiaries receive the proper dose and recommended duration of therapy for their disease state to achieve the optimal outcome of their treated condition, while minimizing potential for adverse events, inappropriate therapy, and wastage.

Special Note about the TRICARE Retail Pharmacy (TRRx) Program: As of June 1, 2004, responsibility for DoD's TRICARE retail pharmacy network passed to a single contractor, Express-Scripts, Inc. (ESI), consolidating all of DoD's regional retail pharmacy contracts into a single national contract. The retail pharmacy quantity limits listed on this page continue to apply under the new contract.

Days Supply of Medication

The TMOP generally dispenses no more than a 90-day supply of medication.

Retail pharmacies generally dispense no more than a 30-day supply of medication. If a patient desires to obtain more than a 30-day supply at a retail pharmacy, he/she must pay an additional cost share for each additional 30-day supply increment, up to a 90-day supply (3 cost shares).

Quantity Limits

The quantity of medication dispensed to a patient is limited to **the lesser of**: (1) the amount of medication expected to be used in a 90-day period (TMOP) or a 30-day period (retail pharmacy network) based on the directions for use on the prescription, or (2) the quantity limit identified in the table below. The amount of medication obtained by a patient from other Military Health System pharmacy points of service will be taken into account in the application of these quantity limits.

Refills

If the amount dispensed is reduced because of an established quantity limit, refills will be authorized unless the item is designated “no refills allowed” in the table below. For example, the TMOP quantity limit for adalimumab (Humira) is six 40-mg prefilled syringes per six-week period. Therefore, if the TMOP receives a prescription written for 18 prefilled syringes of 40 mg adalimumab (Humira) injection with no refills, the prescription will be filled with 6 syringes, the patient will be charged the applicable cost share, and two refills (of 6 syringes each) will be authorized. The patient will be authorized to obtain a refill (for another 6 syringes) 6 weeks after the original prescription was filled, and will be charged the applicable cost share.

Note: Drugs are listed by generic name. Brand name(s) are supplied in parentheses for convenience only. Quantity limits apply to both brand name and generic versions of listed medications.

Quantity limits developed by the DoD P&T Committee may be superceded by applicable federal and/or state laws.

Drug	TMOP Limits	Retail Pharmacy Limits
Antibiotics		
Azithromycin (Zithromax) 250mg tablets	10 tablets per 30 days	10 tablets per 30 days
Azithromycin (Zithromax) 600mg tablets	24 tablets per 90 days	8 tablets per 30 days
Antiemetics		
Aprepitant (Emend) capsules in convenience packs (one 125 mg capsule and two 80 mg capsules)	6 packs per 90 days	2 packs per 30 days
Aprepitant (Emend) 80 mg capsules	12 capsules per 90 days	4 capsules per 30 days
Aprepitant (Emend) 125 mg capsules	6 capsules per 90 days	2 capsules per 30 days
Granisetron (Kytril) 1mg tablets	24 tablets per 90 days	8 tablets per 30 days
Ondansetron (Zofran) (Zofran; Zofran ODT) 4 and 8 mg tablets and orally disintegrating tablets	45 tablets per 90 days	15 tablets per 30 days
Dolasetron (Anzemet) 50 and 100 mg tablets	15 tablets per 90 days	5 tablets per 30 days
Antifungals		
Fluconazole (Diflucan) 150 mg oral tablets	3 tablets per 90 days	1 Tablet per 30 days
Antimigraine Drugs		
Almotriptan (Axert) 6.25 and 12.5 mg tablets	36 tablets per 90 days	12 tablets per 30 days
Dihydroergotamine (Migranal) 1 mL ampules for nasal spray	90 ampules per 90 days	30 ampules per 30 days
Dihydroergotamine 1 mg/ml injection	90 ampules per 90 days (9 boxes of 10 ampules)	30 ampules per 30 days (3 boxes)
Eletriptan (Relpax)	36 tablets per 90 days	12 tablets per 30 days
Frovatriptan (Frova) 2.5 mg tablets	27 tablets per 90 days	9 tablets per 30 days
Naratriptan (Amerge) 1 and 2.5 mg tablets	27 tablets per 90 days	9 tablets per 30 days
Rizatriptan (Maxalt; Maxalt MLT) 5 and 10 mg tablets and orally-disintegrating tablets	36 tablets per 90 days	12 tablets per 30 days
Sumatriptan (Imitrex) 25, 50 mg tablets	54 tablets per 90 days	18 tablets per 30 days
Sumatriptan (Imitrex) 100 mg tablets	27 tablets per 90 days	9 tablets per 30 days
Sumatriptan (Imitrex) injection 6mg/0.5mL autoinjector (syringes)	24 syringes per 90 days	8 syringes per 30 days
Sumatriptan (Imitrex) injection 6mg/0.5mL vials	24 vials per 90 days	8 vials per 30 days
Sumatriptan (Imitrex) 5mg/100 µL and 20 mg/100 µL nasal spray	18 unit dose nasal sprays per 90 days	6 unit dose nasal sprays per 30 days
Zolmitriptan nasal spray 5 mg/100 µL nasal spray	36 unit dose nasal sprays per 90 days	12 unit dose nasal sprays per 30 days
Zolmitriptan (Zomig; Zomig-ZMT) 2.5 and 5 mg tablets and orally-disintegrating tablets	24 tablets per 90 days	8 tablets per 30 days

Drug	TMOP Limits	Retail Pharmacy Limits
Controlled Substances		
Schedule II drugs	NO refills per federal law; state law may impose additional restrictions	
Schedule III and IV drugs	Per federal law, prescriptions may not be filled or refilled for more than 6 months after the date of the prescription or refilled more than 5 times. State law may impose additional restrictions.	
Testosterone buccal system mucoadhesive (Striant)	180 systems per 90 days (3 cartons of 60 systems)	60 systems per 30 days (1 carton of 60 systems)
Fertility Agents		
Follitroprin alpha for injection (Gonal-F) 37.5 IU ampules	96 ampules (3,600 IU) per 30 days - no refills	96 ampules (3,600 IU) per 30 days - no refills
Follitroprin alpha for injection (Gonal-F) 75 IU ampules	48 ampules (3,600 IU) per 30 days - no refills	48 ampules (3,600 IU) per 30 days - no refills
Follitroprin alpha for injection (Gonal-F) 150 IU ampules	24 ampules (3,600 IU) per 30 days - no refills	24 ampules (3,600 IU) per 30 days - no refills
Follitroprin alpha for injection (Gonal-F) 600 IU/mL kit	6 kits (3,600 IU) per 30 days - no refills	6 kits (3,600 IU) per 30 days - no refills
Follitroprin beta for injection (Follistim) 75 IU vials	48 vials (3,600) IU per 30 days - no refills	48 vials (3,600 IU) per 30 days - no refills
Follitropin beta for injection (Follistim AQ) 300 IU vials	12 cartridges (3,600 IU) per 30 days - no refills	12 cartridges (3,600 IU) per 30 days - no refills
Follitropin beta for injection (Follistim AQ) 600 IU vials	6 cartridges (3,600 IU) per 30 days - no refills	6 cartridges (3,600 IU) per 30 days - no refills
Menotropins for injection (Humegon) 75 IU ampules	48 ampules (3,600 IU) per 30 days - no refills	48 ampules (3,600 IU) per 30 days - no refills
Menotropins for injection (Humegon) 150 IU ampules	24 ampules (3,600 IU) per 30 days - no refills	24 ampules (3,600 IU) per 30 days - no refills
Menotropins for injection (Pergonal) 75 IU ampules	48 ampules (3,600 IU) per 30 days - no refills	48 ampules (3,600 IU) per 30 days - no refills
Menotropins for injection (Pergonal) 150 IU ampules	24 ampules (3,600 IU) per 30 days - no refills	24 ampules (3,600 IU) per 30 days - no refills
Menotropins for injection (Repronex) 75 IU vials	48 vials (3,600) IU per 30 days - no refills	48 vials (3,600 IU) per 30 days - no refills
Urofollitropin for injection (Fertinex) 75 IU ampules	48 ampules (3,600 IU) per 30 days - no refills	48 ampules (3,600 IU) per 30 days - no refills
Urofollitropin for injection (Fertinex) 150 IU ampules	24 ampules (3,600 IU) per 30 days - no refills	24 ampules (3,600 IU) per 30 days - no refills
Urofollitropin for injection (Bravelle) 75 IU ampules	48 ampules (3,600 IU) per 30 days - no refills	48 ampules (3,600 IU) per 30 days - no refills
Impotence Agents		
Drug	TMOP Limits	Retail Pharmacy Limits
Alprostadil injection (Caverject, Edex) 5, 10, 20, and 40 mcg syringes (kits) and vials	18 syringes or vials per 90 days	6 syringes or vials per 30 days
Alprostadil intraurethral pellet (Muse) 125, 250, 500, and 1000 mcg pellets	18 pellets per 90 days	6 pellets per 30 days

Drug	TMOP Limits	Retail Pharmacy Limits
Oral phosphodiesterase-5 (PDE-5) inhibitors Sildenafil (Viagra) 25-, 50-, and 100-mg tablets Tadalafil (Cialis) 5-, 10-, and 20-mg tablets Vardenafil (Levitra) 2.5-, 5-, 10-, and 20-mg tablets	18 tablets per 90 days Quantity limit applies collectively to all strengths of sildenafil, tadalafil, and vardenafil. No more than 18 tablets of any combination of these medications per 90-day supply will be dispensed in the TMOP.	6 tablets per 30 days Quantity limit applies collectively to all strengths of sildenafil, tadalafil, and vardenafil.No more than 6 tablets per 30-day supply of any combination of these medications will be dispensed in the retail network
Miscellaneous		
All syringes & needles	600 syringes and/or needles per 90 days	200 syringes and/or needles per 30 days
Adalimumab (Humira) 40 mg prefilled syringes	6 syringes per 42 days (6 weeks) (3 packages of 2 syringes)	4 syringes per 28 days (4 weeks) (2 packages of 6 syringes)
Anakinra (Kineret) 100 mg/0.67 mL single use prefilled syringes	56 syringes per 56 days (8 weeks) (2 packages of 28 syringes)	28 syringes per 28 days (4 weeks) (1 package of 28 syringes)
Glucose test strips (includes blood and urine test strips)	600 strips per 90 days	200 strips per 30 days
Butorphanol (Stadol) metered dose nasal spray 2.5 mL bottles	15mL per 45 days (6 bottles)	10mL per 30 days (4 bottles)
Dornase alpha (Pulmozyme) inhalant solution 2.5 mL ampule	900 mL per 90 days (360 ampules)	300mL per 30 days (120 ampules)
Enfuvirtide (Fuzeon) injection kit	2 kits (60-day supply)	1 kit (30-day supply)
Etanercept (Enbrel) injection 25mg vial	6 weeks supply based on instructions for use on the prescription	4 weeks supply based on instructions for use on the prescription
Fluoxetine 90 mg capsule (Prozac Weekly)	12 capsules per 90 days (3 blister packs)	4 capsules per 30 days (1 blister pack)
Gefitinib tablets (Iressa)	45 tablets per 45 days	30 tablets per 30 days
Imitinab capsules (Gleevec)	45 days supply	general rule applies (30 days supply)
Ketorolac (Toradol) 10mg tablets	20 tablets (5 day supply) per 30 days	20 tablets (5 day supply) per 30 days
Ketorolac (Toradol) injection IV or IM 15mg/mL - 1mL TUBEX® or vial	Not available at TMOP	40 TUBEX® units or vials per 30 days (600 mg - 5 day supply)
Ketorolac (Toradol) injection IV or IM 30mg/mL 1mL TUBEX® or vial	Not available at TMOP	20 TUBEX® units or vials per 30 days (600 mg - 5 day supply)
Ketorolac (Toradol) injection IM 30mg/mL 2 mL (60 mg) TUBEX® or vial	Not available at TMOP	10 TUBEX® units or vials per 30 days (600 mg - 5 day supply)
PEG-filgrastim (Neulasta) 6 mg/0.6 mL injection	1.2 mL per 45 days (2 syringes)	0.6 mL per 21 days (1 syringe)
Tramadol (Ultram) 50 mg tablets; tramadol / acetaminophen (Ultracet) 37.5/325 mg tablets	720 tablets per 90 days	240 tablets per 30 days
Nasal Inhalers		
Beclomethasone (Beconase, Vancenase) 42 mcg nasal inhaler	100.8 gm per 90 days (15 6.7-gm inhalers or 6 16.8-gm inhalers)	33.5 gm per 30 days (5 6.7-gm inhalers or 2 16.8-gm inhalers)

Drug	TMOP Limits	Retail Pharmacy Limits
Beclomethasone AQ (Beconase AQ, Vancenase AQ) nasal inhaler 42 mcg	150 gm per 90 days (6 25-gm inhalers)	50 gm per 30 days (2 25-gm inhalers)
Beclomethasone AQ (Vancenase AQ) nasal inhaler 84 mcg	57 gm per 90 days (3 19-gm inhalers)	19 gm per 30 days (1 19-gm inhaler)
Budesonide (Rhinocort) 32mcg nasal inhaler	42 gm per 90 days (6 7-gm inhalers)	14 gm per 30 days (2 7-gm inhalers)
Budesonide AQ (Rhinocort AQ) 32mcg nasal spray	30 mL per 90 days (3 10-mL inhalers)	10 mL per 30 days (1 10-mL inhaler)
Flunisolide (Nasalide) nasal solution 0.025%	225 mL per 90 days (9 25-mL inhalers)	75 mL per 30 days (3 25-mL inhalers)
Fluticasone (Flonase) 0.05% nasal spray	48 gm per 90 days (3 16-gm inhalers)	16 gm per 30 days (1 16-gm inhaler)
Ipratropium bromide (Atrovent) 0.03% and 0.06% nasal spray	90 mL per 90 days (3 30-mL inhalers or 6 15-mL inhalers)	30 mL per 30 days (1 30-mL inhaler or 2 15-mL inhalers)
Mometasone (Nasonex) nasal inhaler 50mcg	51 gm per 90 days (3 17-gm inhalers)	17 gm per 30 days (1 17-gm inhaler)
Triamcinolone AQ (Nasacort AQ) 55mcg nasal spray	99 gm per 90 days (6 16.5-gm inhalers)	33 gm per 30 days (2 16.5-gm inhalers)
Triamcinolone (Nasacort) 55mcg nasal spray	90 gm per 90 days (9 10-gm inhalers)	30 gm per 30 days (3 10-gm inhalers)
Triamcinolone (Tri-nasal) 50 mcg nasal spray	90 mL per 90 days (6 15-mL inhalers)	30 mL per 30 days (2 15-mL inhalers)
Oral Inhalers and Inhalant Solutions		
Albuterol (AccuNeb) inhalant solution 0.63mg/3mL and 1.25mg/3mL	1650mL per 90 days (22 boxes of 25 = 550 nebules)	600 mL per 30 days (8 boxes of 25 = 200 nebules)
Albuterol (Proventil) 0.083% inhalant solution 3 mL	1650 mL per 90 days (22 boxes of 25 = 550 nebules)	600 mL per 30 days (8 boxes of 25 = 200 nebules)
Albuterol (Proventil) 0.5% inhalant solution 20 mL	180 mL (9 bottles) per 90 days	60 mL (3 bottles) per 30 days
Albuterol (Proventil) 90mcg metered dose inhaler	102 gm per 90 days (6 17-gm inhalers)	34 gm per 30 days (2 17-gm inhalers)
Albuterol HFA (Proventil HFA, Ventolin HFA) 90 mcg	108 gm per 90 days (6 18-gm inhalers or 16 6.7-gm inhalers)	36 gm per 30 days (2 18-gm inhalers or 5 6.7-gm inhalers)
Albuterol sulfate 3 mg / ipratropium bromide 0.5 mg per 3 mL inhalent solution (DuoNeb)	1620 mL per 90 days (540 vials)	540 mL per 30 days (180 vials)
Beclomethasone 42 mcg (Beclovent) oral inhaler	160.8 gm per 90 days (24 6.7-gm inhalers or 9 16.8-gm inhalers)	53.6 gm per 30 days (8 6.7-gm inhalers or 3 16.8-gm inhalers)
Beclomethasone 84 mcg (Vanceril DS) oral inhaler	129.6 gm per 90 days (24 5.4-gm inhalers or 9 12.2-gm inhalers)	43.2 gm per 30 days (8 5.4-gm inhalers or 3 12.2-gm inhalers)
Beclomethasone dipropionate HFA 40 mcg inhalation aerosol (QVar)	87.6 gm per 90 days (12 inhalers)	29.2 gm per 30 days (4 inhalers)

Drug	TMOP Limits	Retail Pharmacy Limits
Beclomethasone dipropionate HFA 80 mcg inhalation aerosol (QVar)	43.8 gm per 90 days (6 inhalers)	33.6 gm per 30 days (2 inhalers)
Bitolterol (Tornalate) 0.8% oral inhaler	90 mL per 90 days (6 inhalers)	30 mL per 30 days (2 inhalers)
Bitolterol (Tornalate) inhalant solution 0.2%	720 mL per 90 days (24 30-mL bottles or 12 60-mL bottles)	240 mL per 30 days (8 30-mL bottles or 4 60-mL bottles)
Budesonide (Pulmicort) oral inhaler	6 inhalers per 90 days	2 inhalers per 30 days
Budesonide 0.25 mg Inhalation Suspension (Pulmicort Respules®)	720 mL per 90 days (12 boxes of 30 Respules®)	240 mL per 30 days (4 boxes of 30 Respules®)
Budesonide 0.5 mg Inhalation Suspension (Pulmicort Respules®)	360 mL per 90 days (6 boxes of 30 Respules®)	120 mL per 30 days (2 boxes of 30 Respules®)
Cromolyn sodium (Intal) oral inhaler 800mcg	85.2 gm per 90 days (9 8.1-gm inhalers or 6 14.2 gm inhalers)	28.4 gm per 30 days (3 8.1-gm inhalers or 2 14.2-gm inhalers)
Cromolyn sodium (Intal) nebulizing solution 20 mg/ 2 mL unit dose ampules	1080 mL per 90 days (9 boxes = 540 ampules)	360 mL per 30 days (3 boxes = 180 ampules)
Flunisolide (Aerobid; Aerobid-M) oral inhaler 250 mcg	63 gm per 90 days (9 inhalers)	21 gm per 30 days (3 inhalers)
Fluticasone (Flovent) 44-, 110-, and 200-mcg oral inhalers	94.8 gm per 90 days (12 7.9-gm inhalers or 6 13-gm inhalers)	31.6 gm per 30 days (4 7.9-gm inhalers or 2 13-gm inhalers)
Fluticasone (Flovent) 50-, 100-, and 250 -mcg Rotadisks®	720 doses per 90 days (12 boxes of 60 Rotadisks®)	240 doses per 30 days (4 boxes of 60 Rotadisks®)
Fluticasone / salmeterol (Advair) powder for inhalation 100 mcg/50 mcg; 250 mcg/50 mcg; and 500 mcg/50 mcg	180 doses per 90 days (3 inhalers)	60 doses per 30 days (1 inhaler)
Formoterol fumarate (Foradil) powder for inhalation 12 mcg	180 doses per 90 days (3 inhalers)	60 doses per 30 days (1 inhaler)
Ipratropium (Atrovent) 0.02% inhalant solution (2.5mL unit dose ampules)	1350 mL per 90 days (21 boxes of 25 ampules [525 ampules] or 18 boxes of 30 ampules [540 ampules] or 9 boxes of 60 ampules [540 ampules])	450 mL per 30 days (7 boxes of 25 ampules [175 ampules] or 6 boxes of 30 ampules [180 ampules] or 3 boxes of 60 ampules [180 ampules]
Ipratropium (Atrovent) oral inhaler 18 mcg	89 gm per 90 days (6 14.7-gm inhalers)	30 gm per 30 days (2 14.7-gm inhalers)
Levalbuterol (Xopenex) inhalant solution 0.63/3 mL or 1.25 mg/3mL ampules	1080 mL per 90 days (15 boxes of 24 ampules [360 ampules] or 4 boxes of 96 ampules [384 ampules])	360 mL per 30 days (5 boxes of 24 ampules [120 ampules] or 2 boxes of 96 ampules [192 ampules])
Metaproterenol (Alupent) inhalant solution 0.4% or 0.6% 2.5mL unit dose ampules	1250 mL per 90 days (18 boxes of 25 ampules [450 ampules] or 5 boxes of 100 ampules [500 ampules])	500 mL per 30 days (6 boxes of 25 ampules [150 ampules] or 2 boxes of 100 ampules [200 ampules])
Metaproterenol (Alupent) inhalant solution 5% 10mL	180 mL per 90 days (18 10-mL bottles or 6 30-mL bottles)	60 mL per 30 days (6 10-mL bottles or 2 30-mL bottles)

Drug	TMOP Limits	Retail Pharmacy Limits
Metaproterenol (Alupent) oral inhaler 650mcg	84 gm per 90 days (12 7-gm inhalers or 6 14-gm inhalers)	28 gm per 30 days (4 7-gm inhalers or 2 14-gm inhalers)
Nedocromil (Tilade) oral inhaler	145.8 gm per 90 days (9 16.2-gm inhalers)	48.6 gm per 30 days (3 16.2-gm inhalers)
Pirbuterol (Maxair) oral Autohaler®	42 gm per 90 days (3 14-gm inhalers or 15 2.8-gm inhalers)	14 gm per 30 days (1 14-gm inhaler or 5 2.8-gm inhalers)
Pirbuterol (Maxair) oral inhaler	153.6 gm per 90 days (6 25.6-gm inhalers)	51.2 gm per 30 days (2 25.6-gm inhalers)
Salmeterol (Serevent DISKUS®) 50mcg oral inhalation powder Please note: production of salmeterol metered dose oral inhalers has been discontinued. The salmeterol dry powder inhaler (Serevent Diskus) is now the only formulation available. Click here for additional information.	180 doses (blister packs) per 90 days (3 boxes of 60 blister packs)	60 doses (blister packs) per 30 days (1 box of 60 blister packs)
Tiotropium bromide (Spiriva HandiHaler) inhalation powder	90 capsules for inhalation per 90 days (3 packages of 30 caps)	30 capsules for inhalation per 30 days (1 package of 30 caps)
Triamcinolone (Azmacort) oral inhaler 20gm	120 gm per 90 days (6 20-gm inhalers)	40 gm per 30 days (2 20-gm inhalers)
Topicals		
Imiquimod (Aldara) 5% cream	36 single use packets per 90 days (3 boxes of 12 packets)	12 single use packets per 30 days (1 box of 12 packets)
Calcipotriene (Dovonex) 0.005% cream or ointment (30-, 60-, or 100-gm Tubes)	900 gm per 90 days	300 gm per 30 days
Calcipotriene (Dovonex) 0.005% solution	900 mL per 90 days (15 60-mL bottles)	300 mL per 30 days (5 60-mL bottles)
Alitretinoin (Panretin) 0.1% gel	180 gm per 90 days (3 60-gm tubes)	60 gm per 30 days (1 60-gm tube)
Becaplermin (Regranex) 0.01% gel (2-, 7.5- or 15-gm tubes)	45 gm per 90 days	15 gm per 30 days
Tazarotene (Tazorac) 0.05% or 0.1% gel (30- or 100-gm tubes)	300 gm per 90 days	100 gm per 30 days

Correction - The next meetings of the DoD P&T Committee have been changed to Tuesday 13 July and Wednesday 14 July, 2004.

Department of Defense Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **20 APRIL 2004**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 20 April 2004 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
CAPT Terrance Egland, MC (via VTC)	DoD P& T Committee Co-chair
COL Mike Heath, MS (For MAJ Travis Watson)	Army
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
LtCol Gordon Wright Bates, Jr, MC	Air Force
Col Phil Samples, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CDR Patrick Marshall	Coast Guard
Rance Hutchings, Pharm.D. (For Dr. Trevor Rabie)	Uniformed Services Family Health Plans (USFHP)
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

Col James E. Cox, Jr. MC	Air Force

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC, USN	Chief Medical Officer Representative, TMA
COL James Young, BSC, USAF	DoD Pharmacy Program Assistant Director, TMA
COL Kent Maneval, MS, USA	Joint Readiness Clinical Advisory Board
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC, USN (via TC)	DoD Pharmacoeconomic Center
CDR Don Nichols, MC, USN	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC, USAF	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
Elaine Furmaga	Department of Veterans Affairs
Four pharmacists	Iraq Ministry of Health

3. **REVIEW MINUTES OF LAST MEETING** – The minutes from the last meeting were accepted as written.

4. **INTERIM/ADMINISTRATIVE DECISIONS** – None

5. **UNIFORM FORMULARY (UF) PROPOSED RULE** – COL William Davies, DoD Pharmacy Program Director, TMA, updated the Committee on the current status of the Uniform Formulary. The final Uniform Formulary Rule was published 1 Apr 2004. It is available at: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/04-7129.htm.

6. **TRICARE RETAIL PHARMACY (TRRx) UPDATE –** Libby Hearin (PEC) updated the Committee on the status of the TRICARE Retail Pharmacy (TRRx) Program implementation. TRRx establishes a retail pharmacy network that will provide outpatient prescription services to TRICARE beneficiaries throughout the United States, Guam, Puerto Rico, and the U.S. Virgin Islands. Express-Scripts, Inc (ESI) is the contractor for TRRx. ESI is also the contractor for the TRICARE Mail Order Pharmacy (TMOP).

   Beneficiary and provider information concerning TRRx is currently available on the TRICARE Pharmacy site (www.tricare.osd.mil/pharmacy) and on ESI's site at www.express-scripts.com. ESI marketing materials include benefit guides, pharmacy information cards, and introductory letters with a list of network pharmacies closest to beneficiaries. Mail-outs to beneficiary households, TRICARE Service Centers, and placement on the TRICARE SMART site (www.tricare.osd.mil/smart) for MTFs begin 22 Apr 2004.

7. **BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES** – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for two new drugs and one new combination product. The Committee also confirmed the status of two new formulations of existing products (see Appendix A).

7. **ENFUVIRTIDE (FUZEON)** – The manufacturer of enfuvirtide (Fuzeon) has discontinued the controlled distribution program for this product. Under the controlled distribution program, enfuvirtide was previously available in the retail network only through a specialty pharmacy (Chronimed) and was not available in the TMOP. MTFs could purchase enfuvirtide through a special arrangement with Chronimed, but were not able to use the prime vendor system to obtain the product.

   The manufacturer reports that shipping to wholesalers started 14 Apr 2004. The product is expected to be available through U.S. retail and specialty pharmacies staring 26 Apr 2004. MTFs should be able to order Fuzeon from wholesalers as of 26 Apr 2004. Additional information is available at www.pec.ha.osd.mil/Controlled_Distribution_Drugs.htm or from the manufacturer's website (www.fuzeon.com) or help line (1-877-438-9366).

   Enfuvirtide is approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. It is given via subcutaneous injection twice daily and may be self-administered by the patient. The Committee will consider Fuzeon for addition to the TMOP Covered Injectables List as soon as it is clear that supplies of enfuvirtide are adequate and that the TMOP will have no difficulty obtaining the product.

9. **SERMORELIN (GEREF, SERONO)** – The Geref brand of sermorelin (growth hormone releasing hormone) has been withdrawn from the market. The diagnostic product (Geref Diagnostic) is still available. Since the therapeutic product is no longer available, the Committee removed sermorelin from the TMOP Covered Injectables List.

10. **KETOROLAC ORAL** – Currently, ketorolac (Toradol) tablets are available from the TMOP with a quantity limit of 5 days supply per 30 days. Express-Scripts does not typically make ketorolac tablets available through mail order plans, so they requested that the Committee consider discontinuing availability of ketorolac tablets at the TMOP. In the 6-month period from Oct 2003 to Mar 2004, the TMOP filled 41 prescriptions for ketorolac tablets, none of which exceeded 20 tablets (a 5-day supply at maximum recommended dosing). The Committee decided that since some patients do fill prescriptions for ketorolac tablets through the TMOP and since there is no indication that patients are receiving excessive quantities of ketorolac, ketorolac tablets will remain on the TMOP Formulary with the current quantity limits.

11. **QUININE** – Quinine has historically been used for nocturnal leg cramps, but this has never been an FDA-approved indication. In 1994-1995, the FDA halted the sale and distribution of OTC quinine sulfate for leg cramps due to its serious risks (Federal Register, 22 Aug 1994). In 1995, the FDA sent letters to manufacturers ordering a halt to the promotion of prescription quinine for leg cramps (FDA Consumer, 1995). In 1998, the FDA halted the sale and distribution of OTC quinine for malaria (Federal Register, 20 Mar 1998). In Feb 1999, the DoD P&T Committee excluded quinine from the National Mail Order Pharmacy (the

previous mail order program), based on the FDA's actions. Since a formulary does not exist in the retail network, the Committee could not take similar action in regard to the availability of quinine in the retail network. Quinine continues to be available in the retail network.

The only FDA-approved indication for quinine is as a prescription drug for the second-line treatment of malaria, but the vast majority of quinine prescriptions are most likely for treatment of leg cramps. Quinine is also available in food products and dietary supplements.

The Committee agreed that drugs available in the TMOP and the retail network should be consistent whenever reasonable and possible. The Committee considered three options:

- Make quinine available without formulary restriction in both TMOP & the retail network (TRRx).
- Subject quinine to formulary restrictions in both TMOP and TRRx.
- Maintain the status quo.

Background

Nocturnal leg cramps are a common problem in elderly patients. Nonpharmacological treatments (e.g., stretching, heat, correction of dehydration or electrolyte imbalances) are considered first-line therapies. Besides quinine, medications that have been used to treat nocturnal leg cramps include gabapentin, verapamil, muscle relaxants, vitamin E, magnesium, and B-complex vitamins.

Efficacy

Two systematic reviews of quinine for leg cramps support its efficacy for this condition:

- In 1995, Man-Son-Hing M et al (BMJ 1995; 310:13-7) reviewed six placebo-controlled cross-over trials including 107 patients, mostly elderly. Patients received 200-300mg quinine sulfate/day over 2- 4 weeks. Compared to placebo, quinine resulted in 8.83 fewer cramps over 4 weeks (95% CI 4.16 , 13.49) based on 5 trials in 82 pts, a relative risk reduction of 43% (95% CI 21%, 65%). There was a 27.5% reduction (95% CI 30.6%, 24.4%) in the number of nights with cramps, based on 2 trials in 51 pts. There was no statistically significant change in the severity or duration of cramps.
- In 1998, Man-Son-Hing M & Wells G, (J Gen Intern Med 1998; 13:600-6) published an updated meta-analysis including pooled individual patient data (combined n=659) from 8 randomized, double-blind, placebo-controlled trials (7 cross-over trials), 4 of which were unpublished. Patients taking quinine had 3.6 (95% CI 2.15 , 5.05) fewer leg cramps over 4 weeks compared to placebo, a relative risk reduction of 21% (95% CI 12% , 30%). Investigators concluded that while publication bias was present (almost all published studies reported higher efficacy than unpublished studies), quinine still appeared to be more effective than placebo in reducing the frequency of nocturnal leg cramps.

Safety/Tolerability

- The FDA's 1994-1995 regulatory actions were based on 157 reports of quinine-associated adverse drug reactions (1969 through mid-1992), 105 of which involved dosing within recommendations. The reports included 16 deaths and 40 hospitalizations.
- Adverse effects at doses used for leg cramps include dizziness, fever, nausea and vomiting, diarrhea, visual or auditory disturbances, and thrombocytopenia (rare but

potentially fatal). Quinine should NOT be used in pregnancy (Category X), should be used with caution in patients with renal failure, and should be avoided in patients with hepatic failure. Patients with a history of immune mediated thrombocytopenia or G-6-PD deficiency should not receive quinine.

- Brinker & Beitz (Am J Hematol 2002; 70:313-7) reported on a case series of thrombocytopenia associated with quinine. Of 397 adverse drug reactions for quinine reported to the FDA from 1974 – 2000, there were 141 reports of apparently isolated thrombocytopenia. After eliminating cases confounded by disease or drug therapy, investigators focused on 64 reports. The typical presentation of thrombocytopenia appeared to be rapid (median time-to-onset 7 days) and severe (hospitalization in 57 cases). Investigators suggested that clinicians evaluating patients with new-onset thrombocytopenia watch for quinine use, including food and dietary supplements.
- Kojouri et al (Ann Intern Med 2001;135:1047-51) reported that 11% of 132 consecutive cases of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) were associated with quinine. They commented that the toxicity appeared immune-mediated, with a sudden onset. Women may be more susceptible than men.
- Quinine has a long half-life, is protein-bound, and is metabolized by CYP450. It has several potentially dangerous drug-drug interactions, including elevation of digoxin levels and increased effect of anticoagulants.

Other Factors

Various criteria, guidelines, and recommendations from published reviews conclude that while quinine should not be used first-line, cautious use may be justified in patients with severe symptoms who have failed other treatments.

- The VA's nonformulary criteria for use (available at www.vapbm.org) recommend reserving use of quinine for nocturnal leg cramps for patients who have failed other modalities and who have severe symptoms requiring treatment. Patients should be advised of the potential for adverse drug reactions.
- Similar advice is provided by the UK National Health System's PRODIGY guidance, (http://www.prodigy.nhs.uk/guidance.asp?gt=Leg%20cramps) which recommends non-drug treatment first-line, with drug treatment only in people with regular cramps significantly affecting quality of life. The guidance suggests that clinicians monitor the risk-benefit ratio with quinine due to the potentially toxic effects.
- The April 2004 Pharmacist's Letter succinctly summarizes the dilemma, suggesting that pharmacists "help people understand pros and cons and decide for themselves…"

Quinine Utilization

- A total of 28,655 DoD beneficiaries received at least one prescription for quinine at MTFs or retail pharmacies in the six months from Oct 2003 to Mar 2004. Of these, 20,557 received quinine prescriptions in retail pharmacies, 8,369 at MTF pharmacies (does not add to 28,655 because some beneficiaries used both points of services).
- Utilization of quinine is increasing, most likely due to the increased numbers of patients 65 years of age and older using the retail network.

The Committee agreed that the non-availability of quinine in the TMOP probably did not decrease the use of quinine for nocturnal leg cramps, since patients could readily fill these prescriptions at retail network pharmacies. The Committee voted to add quinine to the TMOP Formulary. Quinine will be available from the TMOP and retail network without a prior authorization or other formulary restriction. Considerations included:

- Clinical evidence of efficacy of quinine in the treatment of nocturnal leg cramps and the existence of criteria, guidelines, and reviews supporting cautious use in patients for whom the benefits outweigh the considerable risks.
- The absence of an FDA-mandated special distribution process or special monitoring requirements for quinine.
- The incongruence of denying prescriptions for quinine in the TMOP while filling prescriptions for quinine in retail pharmacies.

The Committee noted that the TMOP provides a patient information insert with all medications, including quinine. Patients using the TMOP have access to a toll-free number for pharmacist consultation. Individual providers and pharmacists should assess the patient-specific benefits and risks of this medication and educate patients accordingly.

12. QUANTITY LIMITS

A. *Follitropin beta (Follistim AQ)* – All injectable gonadotropins, including follitropin, currently have a quantity limit of 3600 IU per 30 days (no refills) in both TMOP and the retail network. These products are also subject to prior authorization. Follistim AQ is a new formulation of follitropin beta in a pre-filled, pre-mixed cartridge for use with the "Follistim Pen." It is supplied in a box containing 4 needles and 1 prefilled cartridge containing either 300 or 600 IU of follitropin beta. The Committee established quantity limits for this new formulation consistent with existing products. These quantity limits apply to both TMOP and retail:

   - 300 IU cartridge: 12 cartridges (3600 IU) per 30 days, no refills
   - 600 IU cartridge: 6 cartridges (3600 IU) per 30 days, no refills

B. *Anakinra (Kineret)*- As of 23 Feb 2004, Amgen stopped selling 7-syringe packs of anakinra. Anakinra is now available only as 28-syringe packs (4 weeks supply). The current quantity limit for anakinra in the TMOP is a 6-week supply (6 packages of 7 syringes). The Committee voted to change the quantity limits for anakinra to the following:

   - TMOP: 56 syringes = 2 packages of 28 syringes per 56 days (8 weeks supply);
   - Retail: 28 syringes = 1 package of 28 syringes per 28 days (4 weeks supply)

   The Committee decided to assess the impact of the increased quantity limit on utilization of anakinra before considering any changes to the current 6-week quantity limits for etanercept (Enbrel) and adalimumab (Humira), which are similar injectable agents also used for the treatment of rheumatoid arthritis and available from the TMOP.

13. PRIOR AUTHORIZATIONS (PAS)

A. *Implementation of the Growth Hormone PA* – The Committee recommended implementation of the PA in both TMOP and the retail network as of 1 Jun 2004 for new patients only (i.e., patients presenting a new growth hormone prescription at a retail

network pharmacy or the TMOP for whom there was no prescription fill for growth hormone in the preceding 180 days).

The Committee recommended that patients who are currently receiving growth hormone in the TMOP and retail network (based on use within the last 180 days) should be required to fulfill PA requirements within 180 days after being notified about the existence of the PA. A method to notify patients who are currently receiving growth hormone from the TMOP or a retail network pharmacy has not been finalized.

A total of 1147 DoD beneficiaries received at least one prescription for growth hormone during the six-month period from Oct 2003 to Mar 2004. Of these, 220 received growth hormone prescriptions in retail pharmacies, 443 at MTF pharmacies, and 506 in the TMOP (does not add to 1147 because some beneficiaries used more than one point of service).

14. ADJOURNMENT – The meeting adjourned at 1130 hours. The next meeting is scheduled for 29 and 30 June at the PEC. All agenda items should be submitted to the co-chairs no later than 4 June 2004.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: DOD P&T COMMITTEE FORMULARY DECISIONS REGARDING NEWLY APPROVED DRUGS

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Amlodipine besylate / atorvastatin tablets (Caduet; Pfizer)	2 Feb 2004. Combination tablet approved for patients for whom treatment with both amlodipine and atorvastatin is appropriate; i.e., hyperlipidemia AND hypertension, chronic stable angina, or vasospastic angina Launch date is 27 Apr 2004.	Not added to the TMOP Formulary Atorvastatin is not on the TMOP Formulary due to provisions of the statin contract; amlodipine is available from the TMOP	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Nifedipine sustained release, simvastatin (contract statin)
Epinastine HCl 0.05% ophthalmic solution (Elestat; Allergan)	12 Oct 2003 (not launched until Jan 2004). Topically active antihistamine with mast cell stabilizing properties, indicated for the prevention of itching associated with allergic conjunctivitis.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** There are no ophthalmic antihistamine products on the BCF.
Tiotropium bromide inhalation powder (Spiriva HandiHaler; Boehringer / Pfizer)	30 Apr 2004 (Launch date is not expected until 11 Jun 2004). Tiotropium bromide is an anticholinergic with specificity for muscarinic receptors. It is indicated for the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It is not indicated to relieve dyspnea associated with COPD. The product consists of a capsule containing a dry powder formulation of tiotropium bromide, intended for use with the HandiHaler oral inhalation device.	Added to the TMOP Formulary	**Quantity Limits** TMOP: 90 caps per 90 days (3 packages of 30 caps for inhalation) Retail: 30 caps per 30 days (1 package of 30 caps for inhalation) **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Albuterol MDI; Ipratropium MDI (Atrovent); albuterol /ipratropium MDI (Combivent); salmeterol / fluticasone (Advair Diskus) and salmeterol DPI (Serevent Diskus)
Mycophenolic acid delayed-release tablets (Myfortic; Novartis)	Immunosuppressant approved for the prophylaxis of organ rejection in patients receiving renal transplants. It is administered in combination with cyclosporine and corticosteroids. This product is a new formulation of mycophenolate mofetil (Cellcept).	Added to the TMOP Formulary as a line extension	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** none
Clozapine orally disintegrating tablets (Fazaclo; Alamo Pharmaceuticals)	Clozapine is an atypical antipsychotic agent approved for schizophrenia. This product is formulated as an orally disintegrating tablet.	Not added to the TMOP Formulary. Clozapine is excluded from the TMOP due to monitoring requirements and dispensing restrictions mandated by the FDA.	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Quetiapine (Seroquel) and risperidone (Risperidal)

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE APRIL 2004 DOD P&T EXECUTIVE COUNCIL & DOD P&T COMMITTEE MEETINGS

1. **BCF CHANGES**
   A. *Additions to the BCF - None*
   B. *Deletions, changes, clarifications or exclusions from the BCF*
      1) Fexofenadine (Allegra) was removed from the BCF. There is no longer a second generation antihistamine on the BCF. The BCF now states that MTFs must have at least one second generation antihistamine on their formularies. The Council strongly encourages all MTFs to include loratadine on their formularies.
2. **TMOP FORMULARY CHANGES**
   A. *Additions to the TMOP Formulary*
      1) Epinastine HCl 0.05% ophthalmic solution (Elestat; Allergan)
      2) Tiotropium bromide inhalation powder (Spiriva HandiHaler; Boehringer/Pfizer) – has quantity limits (see Section 3 below)
      3) Mycophenolic acid delayed-release tablets (Myfortic; Novartis)
      4) Quinine
   B. *Exclusions from the TMOP Formulary*
      1) Amlodipine/atorvastatin (Caduet; Pfizer) (combination tablets) – excluded from the TMOP Formulary due to current statin contract
      2) Clozapine orally disintegrating tablets (Fazaclo; Alamo Pharmaceuticals) – excluded from the TMOP Formulary due to monitoring requirements and dispensing restrictions mandated by the FDA
      3) Sermorelin (Geref, Serono) – removed from the TMOP Covered Injectables list
3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**
   A. Quantity limits for follitropin beta injection (Follistim AQ) for both TMOP and retail:
      - 300 IU cartridge: 12 cartridges (3600 IU) per 30 days, no refills
      - 600 IU cartridge: 6 cartridges (3600 IU) per 30 days, no refills
   B. TMOP quantity limits for Anakinra (Kineret) were changed to an 8-week rather than a 6-week supply, to accommodate discontinuation of the 7-syringe pack. Anakinra is now available in 28-syringe packs only. Quantity limits in the retail network remain unchanged.
      - TMOP: 56 syringes = 2 packages of 28 syringes per 56 days (8 weeks supply);
      - Retail: 28 syringes = 1 package of 28 syringes per 28 days (4 weeks supply)
   C. Quantity limits for tiotropium bromide inhalation powder (Spiriva)
      - TMOP: 90 caps per 90 days (3 packages of 30 caps for inhalation)
      - Retail: 30 caps per 30 days (1 package of 30 caps for inhalation)
4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION (PA) PROGRAM**
   A. *Growth Hormone* – The Committee recommended implementation of the PA in both TMOP and the retail network as of 1 Jun 2004 for new patients only (i.e., patients presenting a new growth hormone prescription at a retail network pharmacy or the TMOP for whom there was no prescription fill for growth hormone in the preceding 180 days). A method to notify patients who are currently receiving growth hormone from the TMOP or a retail network pharmacy about the existence of the PA has not been finalized.

Corrections - Page 7 amended to correct prices for formoterol and salmeterol, following initial dissemination of these minutes on 13 May 2004

The next meetings of the DoD P&T Committee have been changed to Tuesday 13 July and Wednesday 14 July, 2004.

Department of Defense Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **20 April 2004**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council convened at 1300 hours on 20 April 2004 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
CDR Terrance Egland, MC (Via VTC)	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS (Via VTC)	Army
LtCol Gordon Wright Bates, Jr., MC	Air Force
Col Phil Samples, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CDR Patrick Marshall	Coast Guard
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

COL James E. Cox, Jr., MC	Air Force

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC	Deputy Chief Medical Officer Representative, TMA
COL Mike Heath, MS, USA (Via VTC)	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
CAPT Betsy Nolan, MSC (Via VTC)	Navy Pharmacy Specialty Leader
COL James Young, BSC, USAF (Via VTC)	DoD Pharmacy Program Assistant Director, TMA
COL Kent Maneval, MS	Joint Readiness Clinical Advisory Board
CDR Don Nichols, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Elaine Furmaga	Department of Veterans Affairs
Four pharmacists	Iraq Ministry of Health

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

None.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARDS, RENEWALS AND TERMINATIONS

A. *New Contracts Awarded* – tramadol (Caraco) and ranitidine (Golden State Medical). The Council encourages MTF pharmacies to order these products from the contracted companies.

B. *Changes to Existing Contracts*

1) The next option year was exercised for contracts on the following drugs: 35 mcg ethinyl estradiol/1 mg ethynodiol diacetate (Pharmacia/Pfizer), zolmitriptan (AstraZeneca), etodolac (Taro), hydrochlorothiazide (Ivax), and glyburide (Pharmacia/Pfizer).

2) Additional NDCs were added to existing contracts for metoprolol 50 mg (Caraco), NDC# 57664-0477-08, and tramadol 50 mg (Caraco), NDC# 57664-0377-13.

3) Contracts for insulin syringes (BD), isosorbide mononitrate (Schwarz), and capsaicin cream (Qualitest) were extended.

4) The contracts for levobunolol, timolol, prazosin, verapamil and nortriptyline have no more options years left. They will be reevaluated for resolicitation.

C. *Contracts Pending Award* – amantadine, enalapril, salsalate, and insulin

D. More information about DoD and DoD/VA national pharmaceutical contracts may be found on the Defense Supply Center Philadelphia (DSCP) DMM-Online website at http://dmmonline.dscp.dla.mil/pharm/contractlist.asp. Contract guidance for the oral fluoroquinolones, statins, leutinizing hormone releasing hormone (LHRH) agonists, and triptans are available on the PEC website at www.pec.ha.osd.mil/national_contracts.htm.

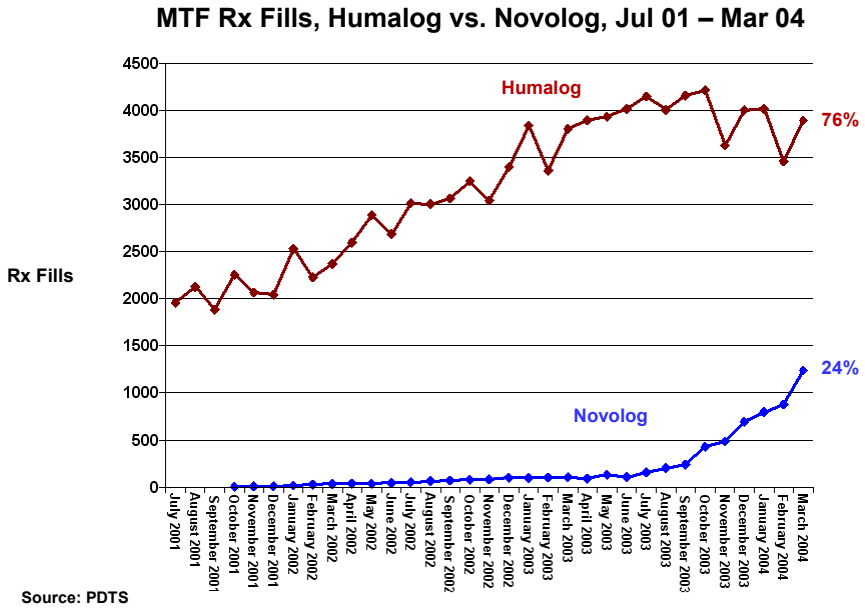
E. The Council reviewed the top 40 drug classes by MTF expenditure for FY 2003. National pharmaceutical contracts or incentive price agreements exist for medications in many of these drug classes. The remaining classes are likely targets for procurement initiatives in the future.

MTF Expenditures by Drug Class,* FY 2003**

Rank	Drug Class	$		Rank	Drug Class	$
1	Antihistamines †	$88 M		21	Metformin †	$22 M
2	NSAIDs †	$86 M		22	Leukotriene antagonists	$21 M
3	Lipotropics †	$83 M		23	Glucocorticoids	$20 M
4	SSRIs †	$64 M		24	Macrolides	$19 M
5	PPIs & H2 blockers †	$61 M		25	Antifungals	$19 M
6	Bisphosphonates †	$45 M		26	Antimalarials	$18 M
7	Calcium channel blockers†	$45 M		27	Hematinics †	$17 M
8	ACE inhibitors †	$43 M		28	Antimigraine agents †	$17 M
9	Vaccines (Hep A & B) †	$38 M		29	Beta-adrenergics (e.g., albuterol) †	$16 M
10	Anticonvulsants †	$37 M		30	Estrogenic agents †	$15 M
11	Salmeterol / fluticasone (Advair)	$31 M		31	Antipsychotics †	$15 M
12	Thiazolidinediones†	$30 M		32	Vaccines/Toxoids	$14 M
13	Quinolones †	$28 M		33	Vaccines, Gram (-) Bacilli	$13 M
14	Antiplatelet agents †	$27 M		34	Bupropion †	$13 M
15	Penicillins	$24 M		35	Miotics / intraocular pressure agents †	$13 M
16	Blood glucose diagnostics †	$24 M		36	Beta blockers †	$12 M
17	Contraceptives †	$23 M		37	Insulins †	$11 M
18	Narcotic analgesics	$22 M		38	ADHD drugs †	$10 M
19	Aqueous nasal steroids †	$22 M		39	Serotonin-norepi reuptake inhibitors	$10 M
20	ARBs	$22 M		40	Sedative/hypnotics	$10 M
Top 20 classes = $843 M 52% of total expenditures				**Top 40 classes = $1,148 M 70% of total expenditures**		

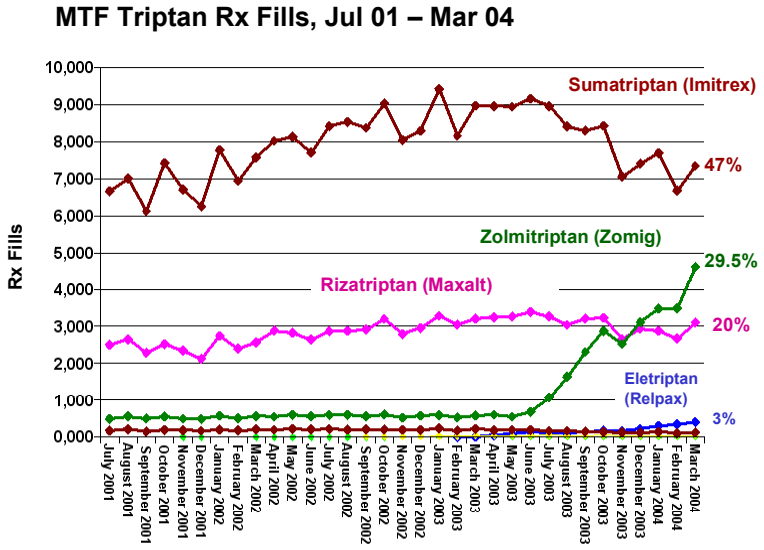
* Drug classes based on First Data Bank HIC-3 classifications
** Expenditures based on DoD Prime Vendor data. May underestimate expenditures in some drug classes, especially products not always ordered through the pharmacy prime vendor system (e.g., vaccines, blood glucose test strips)
† National pharmaceutical contracts or incentive price agreements exist.

F. The Council reviewed utilization of the rapidly-acting insulin analogue products, insulin lispro (Humalog) and insulin apart (Novolog). Due to a voluntary price reduction, Novolog costs only $17.16 per 10 mL vial while the FSS price for Humalog is $31.96 per 10 mL vial. MTFs are saving money by using Novolog rather than Humalog.



Source: PDTS

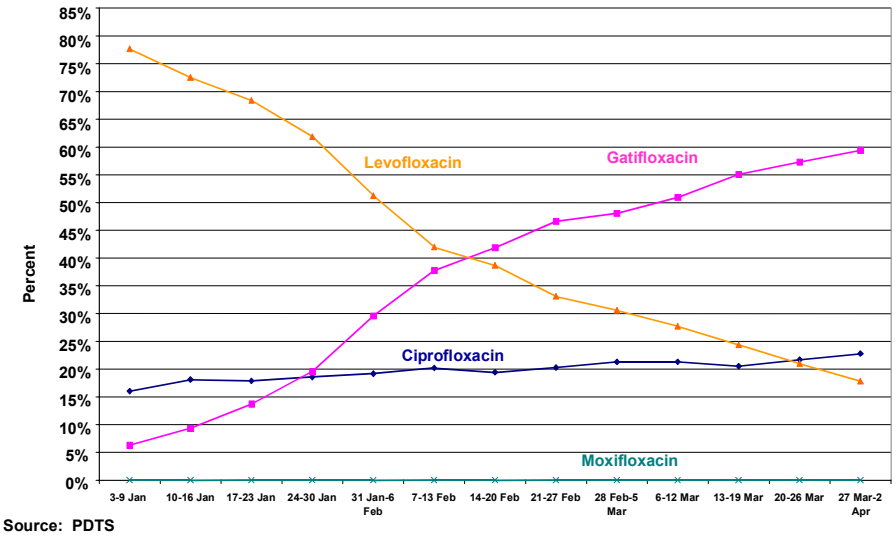
G. The Council reviewed MTF utilization of the triptans and compliance with the joint DoD/VA contract for zolmitriptan. Zolmitriptan at $3.20 per tablet (contract price) costs at least 20% less than any other triptan. Zolmitriptan should be used as the first-line triptan for all new patient starts unless there is a medical necessity to use a different triptan.



Source: PDTS

H. The Council reviewed MTF utilization of the oral fluoroquinolones and compliance with the joint DoD/VA contract for gatifloxacin. Gatifloxacin is the contract oral fluoroquinolone for the treatment of community-acquired pneumonia and sinusitis. The contract price for gatifloxacin 400 mg is $1.35 per tablet, compared to the FSS price of $5.06 per tablet for levofloxacin 500 mg. The following graph shows the weekly MTF market share for each of the oral fluoroquinolones over the last 3 months. As of the week ending 2 April 2004, almost 60% of oral fluoroquinolone prescriptions were for gatifloxacin.

MTF Oral Fluoroquinolone Rx Market Shares, Weeks Ending 8 Jan 04 – 2 Apr 04



Source: PDTS

6. BCF CHANGES AND CLARIFICATIONS

A. *Long Acting Beta Agonists*

CDR Denise Graham and CPT Jill Dacus (PEC) presented an analysis comparing the long-acting beta agonists salmeterol (Serevent Diskus), which is currently on the BCF, and formoterol (Foradil). The Council considered whether formoterol should be added to the BCF and whether salmeterol should be removed from the BCF.

Efficacy/Safety/Tolerability

Formoterol is a long acting beta-2 agonist indicated for the maintenance treatment of asthma, the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, acute prevention of exercise-induced bronchospasm, and maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease (COPD). Clinical studies have shown comparable efficacy with formoterol compared to salmeterol in the maintenance treatment of asthma and the treatment of reversible obstructive airway disease. Safety and tolerability of the two drugs appear similar.

Formoterol has a faster onset of action than salmeterol, but this may not be a significant clinical advantage since salmeterol and formoterol are not indicated for acute bronchoconstriction. Acute bronchoconstriction should be treated with a

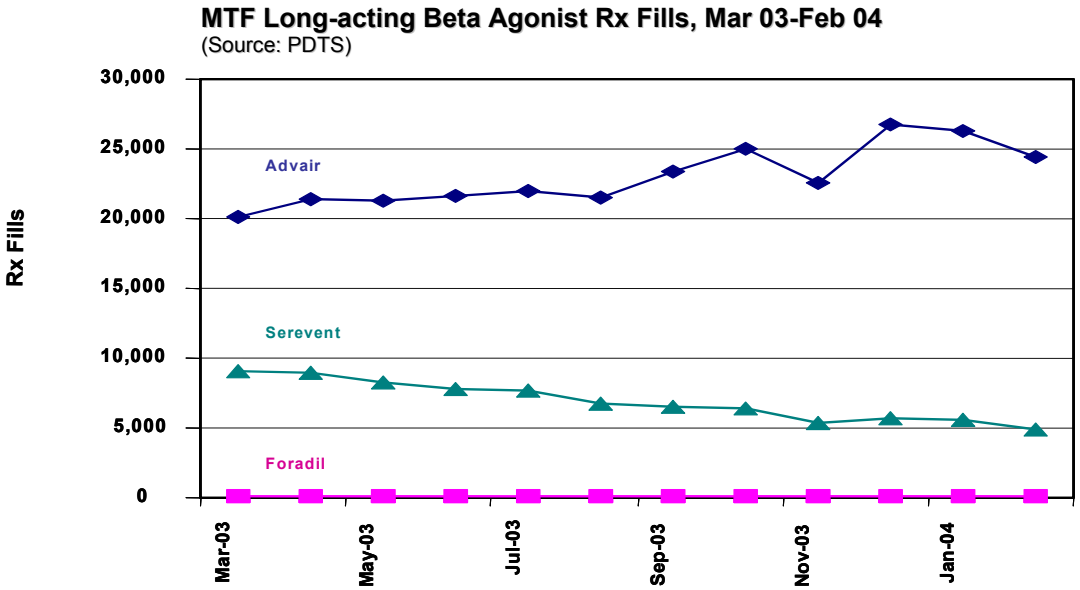
short-acting beta agonist (e.g., albuterol). Salmeterol and formoterol are typically used as adjunctive therapy with inhaled corticosteroids in patients with asthma and with ipratropium in patients with COPD.

Other Factors

- Fewer than 10% of MTFs (14/149) currently have formoterol on formulary. Salmeterol is on the BCF as a single agent (Serevent) and in combination with fluticasone (Advair).
- Patients may find the salmeterol inhaler device (Serevent Diskus) easier to use than the formoterol device (Foradil Aerolizer). Serevent Diskus is packaged as a self-contained dry powder inhaler device preloaded with 28 or 60 doses of 50 mcg of salmeterol. An indicator on top provides the number of doses remaining. Foradil Diskus is a small cylindrical device that is loaded by the patient with a capsule containing 12 mcg of formoterol and squeezed to pierce the capsule. The patient must open the device after inhaling to ensure that the entire dose was delivered. Formoterol capsules come in 12- or 60-count blister packs.
- Salmeterol may be stored at room temperature, and must be used within 6 weeks after opening the foil packet. Formoterol requires refrigeration while stored in the pharmacy, although the patient may store the product at room temperature for up to 4 months after dispensing.

Utilization

As of Feb 2004, MTFs were filling approximately 84 formoterol prescriptions per month, compared to 4,879 prescriptions per month for salmeterol. MTFs fill about 25,000 prescriptions per month for the combination salmeterol/fluticasone product (Advair).



Cost

Based on current FSS prices and recommended dosing regimens, salmeterol costs $44.57 per month compared to $32.63 per month for formoterol. The manufacturer of formoterol has offered a voluntary price reduction for formoterol to all DoD accounts at $31.50 per 60 doses regardless of BCF status. In addition they are offering a MTF based incentive agreement where MTFs can obtain a lower price in exchange for local formulary status and market share performance.

Conclusion

The Council voted unanimously not to add formoterol to the BCF. Long-acting beta agonist usage (as a single agent) is declining steadily. Formoterol may be more difficult for patients to use than salmeterol. Formoterol requires refrigeration prior to dispensing. Formoterol does not offer a significant clinical advantage over salmeterol. Although formoterol costs less than salmeterol, the Council doubted that MTFs would significantly shift usage from salmeterol to formoterol, especially in light of the overall decline in usage of long-acting beta agonists relative to the combination product (Advair). A formoterol/inhaled corticosteroid product (formoterol/budesonide) is not expected until 2006 or later.

The council voted not to remove salmeterol from the BCF in order to maintain uniform availability of a long-acting beta agonist product across MTFs.

7. ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

Bristol Myers Squibb submitted a "pre-award" GAO protest of the blanket purchase agreement (BPA) request for price quotes that the Defense Supply Center Philadelphia (DSCP) issued to pharmaceutical companies that market ARBs. Pending the resolution of this protest, the Council made no final decision regarding the addition of an ARB to the BCF.

8. SECOND-GENERATION ANTIHISTAMINES

The Claritin brand of loratadine is available through a joint DoD/VA blanket purchase agreement for $0.38 per 10-mg tablet. Generic loratadine is available at prices as low as $0.12 per 10-mg tablet and is expected to drop to as low as $0.07 per 10-mg tablet. Fexofenadine 180 mg costs $0.85 per tablet (incentive agreement price for having fexofenadine on the BCF). Fexofenadine 180 mg will likely increase to the FSS price of $1.42 per tablet if fexofenadine is removed from the BCF. The FSS price for cetirizine 10 mg is $0.96 per tablet.

At its February 2004 meeting the Council considered a proposal to remove fexofenadine from the BCF because some MTF pharmacy personnel had stated that the presence of fexofenadine on the BCF inhibits their ability to increase their use of the much less expensive loratadine. The Council voted at that time to keep fexofenadine on the BCF out of concern that MTFs may not shift enough of the market share to loratadine to offset the negative financial impact of a fexofenadine price increase. The Council did not want to remove fexofenadine from the MTF unless there was evidence that MTFs could shift more usage to loratadine.

The loratadine market share at MTFs has risen rapidly since the last meeting. Loratadine accounted for 14% of MTF prescription fills for second generation antihistamines in March 2004—nearly double the 7.5% market share that loratadine had in the first quarter of FY 2004. Loratadine accounted for over 20% of new MTF prescriptions for second generation antihistamines during the first two weeks of April 2004. An April 2004 PEC survey of 209 MTF providers indicated that 2 out of 3 would be willing to prescribe loratadine 1st line if the price was $0.10/tab or less. As of 1 May 2004, loratadine should be available from local wholesalers in bottles of 500 at $0.07/tab.

The Council reviewed several market-share and price scenarios and concluded that MTFs would likely need to achieve a loratadine market share of 25% to 32% in order to break-even financially in the second-generation antihistamine class (depending on the future prices of the second generation antihistamines and their market shares). Based on MTF performance over the last three months in shifting market-share to loratadine, the Council felt confident that MTFs will shift enough market share to loratadine to generate significant savings in this drug class. The Council voted to remove fexofenadine from the BCF, which means there is no longer a second generation antihistamine on the BCF. The BCF will now state that MTFs must have at least one second generation antihistamine on their formularies. The Council strongly encourages all MTFs to include loratadine on their formularies.

9. ADJOURNMENT

The meeting adjourned at 1730 hours. The next meeting is scheduled for 29 and 30 June at the PEC. All agenda items should be submitted to the co-chairs no later than 4 June 2004.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **12 FEBRUARY 2004**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 12 February 2004 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
CAPT Terrance Egland, MC	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
LTC Emery Spaar, MS (For MAJ Travis Watson, MS)	Army
Col Mark Nadeau, MC (For Col Bill Sykora, MC)	Air Force
LtCol Phil Samples, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CDR Patrick Marshall	Coast Guard
Dr. Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

Col John R. Downs, MC	Air Force

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC, USN	Chief Medical Officer Representative, TMA
LTC Bates Gordon, MC, USAF	
COL Kent Maneval, MS, USA	Joint Readiness Clinical Advisory Board
LTC Don DeGroff, MS	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC, USN (via TC)	DoD Pharmacoeconomic Center
CDR Don Nichols, MC, USN	DoD Pharmacoeconomic Center
CDR Jill Pettit, MSC, USN	DoD Pharmacoeconomic Center
HM1 Lisa Drumm	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC, USAF (Via TC)	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke (via TC)	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
Howard Mazzafro	Express Scripts
Debbie Khachikian	Department of Veterans Affairs
Paul Vasquez	Defense Supply Center Philadelphia
Gene Lakey	TriWest
Rance Hutchings, Pharm.D.	Uniformed Services Family Health Plans (USFHP)
Capt Garrett Heitmann, BSC, USAF	Pharmacy Practice Resident

3. **REVIEW MINUTES OF LAST MEETING** – The minutes from the last meeting were accepted as written.

4. **INTERIM/ADMINISTRATIVE DECISIONS** – None

5. **UNIFORM FORMULARY (UF) PROPOSED RULE** – COL William Davies, DoD Pharmacy Program Director, TMA, updated the Committee on the current status of the Uniform Formulary and revisions to the DoD P&T Committee Charter. The FY 2004 National Defense Authorization Act changes the membership of the DoD P&T Committee to include only government members. The DoD P&T Committee will therefore not be subject to the provisions of the Federal Advisory Committee Act (FACA), which would have required public meetings of the DoD P&T Committee. Non-government entities will have a chance to review and comment on recommendations made by the Committee as part of the Beneficiary Advisory Panel, which will include representatives from non-government organizations and associations representing the views and interests of a large number of beneficiaries. Meetings of the Beneficiary Advisory Panel will be held in accordance with FACA.

6. BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 8 new drugs or formulations (see Appendix A).

7. MAIL ORDER AND RETAIL NETWORK ISSUES

A. *Pegvisomant (Somavert)* –The Committee removed pegvisomant from the TMOP Covered Injectables List. Pegvisomant is subject to a controlled distribution process and it is not feasible to provide it through the TMOP.

B. *Desmopressin acetate (DDAVP) injection* – The Committee added desmopressin (DDAVP) injection to the TMOP Covered Injectables List.

C. *Use of Non-Formulary Drugs* – The Committee reviewed utilization of non-formulary drugs in the TMOP: atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin extended release (Altocor), rosuvastatin (Crestor), and esomeprazole (Nexium). Non-formulary drugs are supposed to be available from the TMOP only when the TMOP contractor validates that there is a medical necessity to use the non-formulary drug in lieu of a formulary drug. When Express-Scripts receives a prescription for a non-formulary drug, they contact the prescriber (typically by fax) and attempt to change the non-formulary drug to a formulary drug or obtain information that validates the medical necessity to use the non-formulary drug. The prescription is returned to the patient unfilled if they are unable to contact the prescriber. The Committee noted that use of esomeprazole and the lower strengths of atorvastatin were higher in the TMOP than expected. The Committee asked the PEC to work with Express-Scripts to review the criteria that are used to validate the medical necessity of using non-formulary drugs and revise the criteria if necessary.

8. PRIOR AUTHORIZATIONS (PAs)

A. *PDE-5 Inhibitors* – Health Affairs Policy 98-040, "Practice Guidelines for the Evaluation of Patients Requesting Sildenafil, (Viagra), for the Treatment of Male Impotence" applies to tadalafil (Cialis). The Committee approved changes to the PA criteria for PDE-5 inhibitors to include tadalafil (Cialis). Please see Appendix A for details.

B. *Growth Hormone* – On July 23rd 2003 the FDA approved Humatrope (somatropin [rDNA origin] for injection) as a treatment for non-growth hormone dependent short stature, also known as idiopathic short stature (ISS). Treatment of ISS is not considered medically necessary, and thus is not covered by TRICARE.

CDR Don Nichols (PEC) presented proposed PA criteria for the use of growth hormone in adults and children. The PA criteria were developed by reviewing the literature, preparing draft criteria, soliciting interactive review and comment from a group of approximately 22 pediatric and adult endocrinologists, and then fine-tuning the criteria and TMOP prior authorization form. The Committee approved the criteria outlined below for the retail and mail order (TMOP) points of service:

- Coverage provided for:
  - Growth Hormone Deficiency in children and adults as a result of pituitary disease, hypothalamic disease, surgery or radiation therapy

- Chronic renal insufficiency before renal transplantation with associated short stature
- Other known renal indications: autorecessive polycystic kidney disease, cystinosis and hypophosphatemic rickets in the pediatric population
- Short stature in patients with Turner Syndrome or Prader-Willi syndrome
- Infants born small for gestational age that have not reached age appropriate height by 24 months of age
- Human immunodeficiency virus-associated wasting in adults

- Coverage NOT provided for:
  - Idiopathic Short Stature
  - Depression, Aging or Obesity

The growth hormone PA will not be implemented until a beneficiary notification process has been finalized as part of implementation of the TRICARE Retail Pharmacy (TRRx) contract. A one-year grace period will be allowed for patients who previously received growth hormone to obtain a PA once beneficiary notification has been implemented. A copy of the growth hormone PA form is included as Appendix C, but the form will not be posted on the PEC website until the PA process is implemented. MTFs are encouraged to adopt the growth hormone PA criteria in order to increase the uniformity of the pharmacy benefit across all points of service. MTFs should be aware that under the portable prior authorization process, patients who receive growth hormone at MTFs would be automatically approved to receive growth hormone at TMOP or retail.

C. *Efalizumab Injection (Raptiva*) – Capt Jill Dacus (PEC) presented information to the Committee regarding efalizumab, a biologic agent recently approved by the FDA for the treatment of chronic moderate to severe plaque psoriasis in adults $\geq$ 18 years old. Efalizumab is an IgG1 humanized monoclonal antibody to the alpha chain of CD11a of leukocyte function associated antigen type 1 (LFA-1) that inhibits activation of T-cells, interferes with their adhesion to the endothelium, and slows T-cell migration. Efalizumab is administered via subcutaneous injection at a maintenance dose of 1 mg/kg per week; patients may self-administer efalizumab after training.

Adverse effects noted during clinical trials with efalizumab include a typical "first dose" reaction (headache, chills, fever, nausea, and myalgia within 2 days following the first two injections), rare thrombocytopenia (0.3% of patients [8/2762] experienced platelets < 52,000 mm^3), and an increase in serious infection rate compared to placebo (0.4% vs. 0.1%). There was also a slight excess of malignancies in patients receiving efalizumab (1.8 per 100 patient-years vs. 1.6 per 100 patient-years with placebo); it is not clear if this represents a true increase in risk. Less than 1% of patients discontinued treatment due to adverse effects. Of note is the observation that patients discontinuing treatment tended to have poorer results on restarting treatment.

The Committee considered the following to determine whether or not to institute a PA for efalizumab, and to establish criteria.

- Other biologic agents, including etanercept, adalimumab, and anakinra, all have prior authorization criteria.
- MTF dermatologists surveyed agreed that efalizumab's place in therapy should be second line after topicals, phototherapy and systemic therapy, and that dermatologists should recommend therapeutic intervention with efalizumab based on the extent and severity of plaque psoriasis.
- Efalizumab has a very narrow indication due to the specificity of its action, and should be used only for chronic moderate to severe plaque psoriasis.
- Since efalizumab inhibits T cells, it should be not be used in children whose immune systems may still be maturing.
- Efalizumab is an immunosuppressant and should not be used in conjunction with other immunosuppressive medications, or in patients whose immune systems are otherwise suppressed.
- Like other biologic agents, treatment with efalizumab is costly (about $10,000 per year based on FSS pricing).

The Committee placed efalizumab on the TMOP Covered Injectable List with the PA criteria listed below. The Committee did not establish special quantity limits for efalizumab; patients may obtain up to a 90-day supply at the TMOP and up to a 30-day supply at retail network pharmacies.

- Coverage provided for:
  - Adults (age ≥ 18 years) with chronic moderate to severe plaque psoriasis, defined as a minimum body surface area involvement of 10% OR a body surface area involvement of less than 10%, but in critical areas (e.g. palms, soles or face) and interfering with day-to-day activities

    AND
  - Have tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR are not candidates for phototherapy or systemic therapy

    AND
  - A dermatologist recommends treatment with efalizumab.
- Coverage NOT provided for:
  - Immunocompromised patients or those receiving immunosuppressive agents. These patients should not receive concurrent therapy with efalizumab because of the possibility of increased risk of infections and malignancies.
  - Children (age < 18 years)
  - Patients with psoriatic arthritis without plaque psoriasis

TMOP prior authorization form for efalizumab injection (Raptiva) is available on the PEC website at http://www.pec.ha.osd.mil/PA_Criteria_and_forms.htm.

D. *Revision of Prior Authorization Forms* - The Committee agreed that the TMOP prior authorization forms should include language whereby the prescriber certifies that all information on the form is accurate. The wording of the statement will be coordinated with TMA legal counsel and Express-Scripts. The Committee also agreed that the term "benefit" used in the PA forms should be changed to "coverage," since PA criteria do not determine what the TRICARE benefit is, but do establish criteria under which drugs are covered or not covered.

E. *Cox II Inhibitors* – The Committee voted to discontinue the TMOP PA for COX-2 inhibitors after considering the following:

- The costs of processing COX-2 inhibitor PAs in the TMOP probably exceed any cost-savings that are generated by the PA process.
  - About 88% of COX-2 inhibitor PAs are approved on first review, with an additional 2% approved upon resubmission. It costs DoD more to process the PAs than DoD saves by not filling 10% of the prescriptions submitted.
  - Given the absence of a PA for COX-2 inhibitors in the retail network, the PA process in the TMOP probably shifts some prescriptions to the retail network where the drug acquisition cost is the highest.
  - Although it is impossible to accurately estimate the cost-savings due to the sentinel effect of the PA (i.e., when the requirement to obtain prior authorization causes a provider to refrain from writing a prescription for the drug), the sentinel effect probably does not outweigh the cost of processing the PAs and the incremental cost of shifting prescriptions to the retail network.
- We should not continue the incongruity of having a PA for COX-2 inhibitors in the TMOP but not having a PA for COX-2 inhibitors in the retail network. The administrative burden of instituting a PA for COX-2 inhibitors in the retail network would further complicate the impending implementation of the TRICARE Retail Pharmacy (TRRx) contract and the Uniform Formulary. Discontinuing the COX-2 inhibitor PA in the TMOP will reduce the administrative burden.
- COX-2 inhibitors could possibly be competed for formulary position on the Uniform Formulary. DoD will likely save more money by competing COX-2 inhibitors for formulary position than attempting to institute a PA in the retail network.

The Committee emphasized that removing the PA requirement for COX-2 inhibitors in the TMOP does not mean that MTFs should discontinue their efforts to target the usage of COX-2 inhibitors toward patients who are at high risk for gastrointestinal adverse effects.

9. ADJOURNMENT – The meeting adjourned at 1230 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Tuesday, 20 April 2004. This meeting would normally be held in May, but the meeting will be held in April in order to accommodate training of Iraqi pharmacists in formulary management procedures. All agenda items should be submitted to the co-chairs no later than 19 March 2004.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: DOD P&T COMMITTEE FORMULARY DECISIONS REGARDING NEWLY APPROVED DRUGS

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Alfuzosin HCL extended release tablets (Uroxatral; Sanofi)	12 Jun 03: Indicated for the treatment of signs and symptoms of BPH. Not indicated for treating hypertension. Alfuzosin selectively blocks post-synaptic alpha1 receptors in the prostate.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** The alpha-blockers terazosin and prazosin are on the BCF (mandatory source contracts). Doxazosin and tamsulosin are not on the BCF.
Efalizumab injection (Raptiva; Genentech)	27 Oct 03. Injectable biologic monoclonal antibody. Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The 1 mg/kg dose is administered SQ weekly, but must be reconstituted from single-use 125 mg vials.	Added to the TMOP Formulary and TMOP Covered Injectables List	**Quantity Limits** General rule applies **Prior Authorization** Yes. See Paragraph 8C for criteria and further discussion	Not added to the BCF **Similar BCF agents:** There are no injectable products for psoriasis on the BCF.
Notes Regarding Efalizumab: Efalizumab is the only biologic approved for psoriasis that can be self-administered by subcutaneous injection. Another biologic product, alefacept [Amevive; Biogen] is approved for psoriasis, but it is typically administered as an IM injection in the physician office or clinic. The FSS cost of one efalizumab vial is $204, resulting in an anticipated yearly cost of $10,608.				
Eplerenone tablets (Inspra; Pfizer)	10 Oct 03: Aldosterone antagonist approved to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction <40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. Eplerenone is also indicated for hypertension, and may be used alone or in combination with other anti-hypertensive agents.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Another aldosterone antagonist, spironolactone, is on the BCF.
Estradiol / levonorgestrel transdermal system (Climara Pro; Berlex)	28 Nov 03: Combination estrogen / progestin patch applied once weekly for hormonal replacement therapy. It is indicated for treatment of moderate-to-severe vasomotor symptoms associated with menopause in women with an intact uterus. It is not indicated for osteoporosis.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** There are no combination estrogen/progestin patches on the BCF. The estrogen patch Esclim is on the BCF.

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Lansoprazole delayed release capsule / naproxen tablets kit (Prevacid NapraPAC; TAP)	28 Nov 03: Combination package of lansoprazole with naproxen. Available in 15 mg lansoprazole with either 375 mg or 500 mg of naproxen. Indicated for risk reduction of NSAID-associated gastric ulcers in patients with a history of documented gastric ulcer who require the use of an NSAID in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Supplied as a weekly blister card; packages contain 28 days of therapy.	Not added to the TMOP Formulary	**Quantity Limits** N/A **Prior Authorization** N/A	Not added to the BCF **Similar BCF agents:** The components of this co-packaged combination are on the BCF: lansoprazole capsules (BPA price), and naproxen tablets (mandatory generic sole source contract).
Notes Regarding Lansoprazole/Naproxen: Prevacid NapraPAC co-packages existing dosage forms/strengths of naproxen and lansoprazole together; it does not combine the two ingredients in a single dosage form. The product is intended to facilitate prophylaxis of NSAID-associated gastrointestinal events (e.g., GI bleeding) with a PPI. The Committee's primary concern about this product arose from its cost relative to the individual components, both of which are on the BCF. A BPA price of $0.65 per capsule is in effect for lansoprazole, while naproxen tablets cost $0.05-$0.06, depending on strength (generic sole source contract pricing). An FSS price for Prevacid NapraPAC was not yet available at the time of the meeting. While the FSS price for Prevacid NapraPAC will doubtless be much lower than the prime vendor pricing in effect at the time of the meeting ($3.67 per day), it is not yet clear if the product will cost substantially more than the current $0.75-0.77 per day for naproxen plus lansoprazole, based on BPA and contract pricing. Due to the prospect of excessive cost and the Committee's doubts about the value of the packaging, Prevacid NapraPAC was not added to the TMOP formulary. The Committee was unable to isolate any circumstance in which it would be considered clinically necessary for a patient to receive the co-packaged product rather than lansoprazole and naproxen in separate packaging.			
Memantine tablets (Namenda; Forest)	16 Oct 03: Indicated for the treatment of moderate to severe Alzheimer's Disease (AD). Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist with a chemical structure unrelated to that of other available AD agents, including the cholinesterase inhibitors.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** There are no NMDA receptor antagonists on the BCF. Donepezil (Aricept), a cholinesterase inhibitor indicated for the treatment of mild to moderate Alzheimers, was added to the BCF at the 11 February 2004 DoD P&T Executive Council Meeting
Notes Regarding Memantine: Memantine is the first product labeled for use in patients with moderate to severe Alzheimer's disease. The cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) are labeled for use in patients with mild to moderate disease. Memantine has been studied both as monotherapy and in combination with cholinesterase inhibitors. Monotherapy studies showed a statistically significant slowing in cognitive and functional decline in patients with moderate to severe AD treated with memantine compared to placebo. Required caregiver time was significantly less for memantine treated patients than placebo, with a difference between groups of 45.8 hours per month. The clinical trial comparing combination therapy (donepezil plus memantine) vs. donepezil plus placebo in moderate to severe AD, showed patients on the combination therapy experienced significantly better outcomes than patients treated with donepezil and placebo on measures of cognition, activities of daily living, global outcomes, and behavior. It is unclear if combination therapy provides sufficiently improved outcomes to justify the incremental cost.			

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Olanzapine / Fluoxetine capsules (Symbyax: Lilly)	2 Jan 03: Combination of olanzapine (atypical antipsychotic) and fluoxetine (SSRI) in the same capsule. Symbyax is indicated for the treatment of depressive episodes associated with bipolar disorder.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF. The BCF listing for fluoxetine was clarified to exclude Symbyax. **Similar BCF agents:** The atypical antipsychotics quetiapine and risperidone are on the BCF. There are multiple SSRIs on the BCF, including fluoxetine.
Notes Regarding Olanzapine/Fluoxetine: Olanzapine / fluoxetine capsules (Symbyax) are available in 6 mg or 12 mg olanzapine in combination with either 25 or 50 mg of fluoxetine. Single ingredient tablets of olanzapine (Zyprexa) come in 2.5, 5, 7.5, 10 or 15 mg; fluoxetine capsules are available in 10, 20, or 40 mg. The FSS prices for Symbyax are consistent with those for olanzapine, on a cost / mg basis.				
Tadalafil (Cialis; Bayer/ GSK)	21 Nov 03. Approved for the treatment of erectile dysfunction.	Not added to the TMOP formulary	**Quantity Limits** *TMOP:* 18 tablets of any combination of the three oral PDE-5 inhibitors per 90 days (collective quantity limit). *Retail:* 6 tablets of any combination of the three oral PDE-5 inhibitors per 30 days (collective quantity limit). **Prior Authorization** Yes, see notes below.	Not added to the BCF **Similar BCF agents**: There are no PDE-5 Inhibitors on the BCF.

Notes Regarding Tadalafil: Tadalafil is the third phosphodiesterase-5 (PDE-5) inhibitor to reach the market. It is similar to sildenafil (Viagra) and vardenafil (Levitra) in terms of efficacy and safety; the primary differences are a longer onset of action (45 minutes vs ~ 27 minutes with sildenafil and vardenafil) and duration of action (36 hours vs 4 hours with sildenafil and vardenafil).

Concomitant use of all 3 PDE-5 inhibitors is contraindicated with nitrates due to the risk of hypotension. Labeling for the three products differs with respect to concomitant use with alpha blockers. Tadalafil is contraindicated for use with alpha blockers, with the exception of tamsulosin (Flomax) 0.4 mg. Concomitant use of vardenafil is contraindicated with alpha blockers. Sildenafil labeling does not contain a contraindication for concomitant use with alpha blockers, although a warning against concomitant use of sildenafil at doses above 25 mg within 4 hours of taking an alpha blocker is listed under precautions in the package labeling.

- **TMOP & Retail Network**: Tadalafil will have the same non-formulary status in the TMOP as sildenafil and vardenafil. The three oral PDE-5 inhibitors will be available only if prior authorization criteria are met. Tadalafil will be subject to the same prior authorization process as sildenafil and vardenafil, consistent with guidelines in the Health Affairs Sildenafil Policy. A quantity limit of 18 tablets per 90 days will apply in the TMOP. A quality limit of 6 tablets per 30 days will apply in the retail network. The quantity limit will apply collectively to all oral PDE-5 inhibitors. This means that no more than 6 tablets per 30-day supply of any combination of these medications will be dispensed in the retail network and no more than 18 tablets per 90-day supply will be dispensed in the TMOP.
- **BCF & MTF Formularies:** Guidelines listed in the Health Affairs Sildenafil Policy will also apply to vardenafil and tadalafil.

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE NOVEMBER 2003 DOD P&T EXECUTIVE COUNCIL & THE DOD P&T COMMITTEE MEETINGS

1. **BCF CHANGES**
   A. *Additions to the BCF*
      1) Gatifloxacin oral (does not include the parenteral formulation)
      2) Bupropion sustained release 100- and 150-mg tablets
      3) Donepezil 5- and 10-mg tablets
   B. *Deletions, changes, clarifications or exclusions from the BCF*
      1) Levofloxacin oral was removed from the BCF
      2) The current BCF listing for prednisolone oral was clarified to specify prednisolone 15 mg/5 mL oral syrup
2. **TMOP FORMULARY CHANGES**
   A. *Additions to the TMOP Formulary*
      1) Alfuzosin tablets (Uroxatral)
      2) Efalizumab (Raptiva) injection – requires prior authorization, added to TMOP Covered Injectables List
      3) Eplerenone tablets (Inspra)
      4) Estradiol/levonorgestrel transdermal patch (ClimaraPro)
      5) Memantine (Namenda)
      6) Olanzapine/fluoxetine capsules (Symbyax)
      7) Desmopressin acetate (DDAVP) injection – added to TMOP Covered Injectables List
   B. *Exclusions from the TMOP Formulary*
      1) Lansoprazole/naproxen (co-packaged as Prevacid NapraPAC)
      2) Tadalafil (Cialis) – same non-formulary status in TMOP as sildenafil; available from the TMOP if prior authorization criteria are met. Quantity limits apply (see below).
3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**
   A. Quantity limits for vardenafil tablets (Levitra) – will apply collectively to all oral PDE-5 inhibitors, including sildenafil (Viagra) and tadalafil (Cialis).
      - TMOP: 18 tablets per 90 days (any combination of oral PDE-5 inhibitors)
      - Retail: 6 tablets per 30 days (any combination of oral PDE-5 inhibitors)
4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION (PA) PROGRAM**
   A. Vardenafil will be subject to the same prior authorization process as sildenafil, consistent with guidelines in the Health Affairs Sildenafil Policy.
   B. The COX-2 PA was discontinued (please see Section 8E for more information).
   C. A PA was instituted for efalizumab (Raptiva)
   D. The Committee approved PA criteria for growth hormone, however implementation was delayed due to communication issues related to the TRRx contract.

APPENDIX C: TMOP PRIOR AUTHORIZATION FORM FOR GROWTH HORMONE

Growth Hormone Prior Authorization Request Form

To be completed and signed by the prescriber. To be used only for prescriptions which are to be filled through the Department of Defense (DoD) TRICARE Mail Order Pharmacy (TMOP). Express Scripts is the TMOP contractor for DoD.

Your patient receives their prescription drug benefit from the Department of Defense (DoD). The DoD prescription drug benefit plan requires that we review certain requests for coverage with the prescribing physician. You have prescribed a medication for your patient that requires Prior Authorization before benefit coverage can be provided. Before giving the prescription to the patient, please make a copy of this form, complete the following questions and give the completed form, along with the prescription, to the patient. Please instruct the patient to send this completed form, along with the prescription, to Express Scripts for processing. If Express-Scripts already has your patient's prescription and has requested that you complete this form, the completed form may be faxed to: (877) 895-1900 (toll-free) or (602) 586-3911 (commercial). A copy of this form and explanations of the underlying clinical rationale and criteria for approval are available at http://www.pec.ha.osd.mil/PA_Criteria_and_forms.htm.

Drug for which Prior Authorization is requested: Growth Hormone _____

Step 1 **Please complete patient and physician information (Please Print)**

Patient Name:		Physician Name:	
Address:		Address:	
Member #:		Phone #:	
		Secure Fax #:	

Step 2 **Please complete the clinical assessment**

1. Is the patient a child (<18 years old)?	☐ Yes Please proceed to question 5	☐ No Please proceed to question 2
2. Is the patient an adult with lowered growth hormone levels secondary to the normal ageing process, obesity or depression?	☐ Yes Coverage not approved	☐ No Please proceed to question 3
3. Is the patient an adult with growth hormone deficiency as a result of pituitary disease, hypothalamic disease, trauma, surgery, or radiation therapy, acquired as an adult or diagnosed during childhood?	☐ Yes Coverage approved	☐ No Please proceed to question 4
4. Does the patient have Short Bowel Syndrome or Acquired Immunodeficiency Syndrome (AIDS) wasting or cachexia?	☐ Yes Coverage approved	☐ No Coverage not approved
5. Is the patient a child with non-growth hormone deficient short stature (Idiopathic Short Stature)?	☐ Yes Coverage not approved	☐ No Please proceed to question 6
6. Is the patient a child with growth hormone deficiency, Turner's Syndrome, Prader-Willi Syndrome, chronic renal insufficiency (or other known renal indications) or a child born small for gestational age whose epiphyses have not closed?	☐ Yes Please proceed to question 7	☐ No Coverage not approved
7. Has the patient been evaluated by a pediatric endocrinologist or nephrologist who recommends therapeutic intervention and will manage treatment?	☐ Yes Coverage approved	☐ No Coverage not approved

Step 3 **I certify the above is correct and accurate to the best of my knowledge**

Please sign and date:

_____ _____

Prescriber Signature Date

Latest revision: February 2004

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **11 February 2004**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council convened at 0800 hours on 11 February 2004 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
LTC Emery Spaar, MS (For MAJ Travis Watson, MS)	Army
COL John R. Downs, MC	Air Force
Col Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol Phil Samples, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CDR Patrick Marshall	Coast Guard
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC	Deputy Chief Medical Officer Representative, TMA
Howard Altschwager	Deputy General Counsel, TMA
Paul Vasquez	Defense Supply Center Philadelphia
COL Kent Maneval, MS	Joint Readiness Clinical Advisory Board
CAPT Don Nichols, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC (via telephone)	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC (via telephone)	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke (via telephone)	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Debbie Khachikian	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

The DoD Pharmacy and Therapeutics Executive Council held an interim meeting by email on 8 January 2004 and voted to add gatifloxacin (Tequin) to the Basic Core Formulary (BCF) and remove levofloxacin from the BCF. These BCF changes were made in response to a joint DoD/VA open class contract for gatifloxacin that became effective 15 January 2004 and in response to levofloxacin price increases. The contract designates gatifloxacin as the "workhorse" fluoroquinolone on the BCF for the indications of community acquired pneumonia and acute sinusitis at a contract price of $1.35/tablet for all oral dosage strengths. The levofloxacin 500 mg price increased from $2.01 to $5.06 on 31 January 2004. The Council concurred with the contract implementation guidance that the PEC previously issued to MTFs (www.pec.ha.osd.mil/national_contracts.htm). In light of the large price increase for levofloxacin, MTFs should remove levofloxacin from their formularies. Levofloxacin should only be used in cases of medical necessity—when gatifloxacin and other fluoroquinolones will not meet the clinical need of a patient. MTFs must rapidly decrease their use of levofloxacin in order to maximize the potential cost savings from the gatifloxacin contract.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARDS, RENEWALS AND TERMINATIONS

A. The next option year was exercised for contracts on the following drugs: colchicine, micronized glyburide, goserelin, ibuprofen, lactulose, permethrin and verapamil.

B. The next option year was not exercised for Forest Pharmaceutical's diltiazem (Tiazac) sustained release due to availability of an AB-rated generic at $0.26 per capsule from Inwood, Forest's generic product line. The generic price became effective 15 December 2003 for the following strengths and NDCs:

Diltiazem SA 120mg Capsules	00259-3687-90	#90	$23.40
Diltiazem SA 180mg Capsules	00259-3688-90	#90	$23.40
Diltiazem SA 240mg Capsules	00259-3689-90	#90	$23.40
Diltiazem SA 300mg Capsules	00259-3690-90	#90	$23.40
Diltiazem SA 360mg Capsules	00259-3691-90	#90	$23.40

C. DSCP signed incentive agreements for Aranesp, Amgen's darbepoetin alfa, and Betaseron, Berlex's interferon beta-1b. The exact content and considerations offered in these agreements can be obtained from local Amgen or Berlex representatives or a copy can also be obtained via e-mail by directing a request to Ted.Briski@amedd.army.mil.

D. Incentive agreements are available on the DSCP website at http://dmmonline.dscp.dla.mil/pharm/incentives.asp. Incentive agreements currently apply to the products listed below. MTFs should ensure they are receiving the correct price for these products:

Alendronate (Fosamax)
Azathioprine (Imuran)
BG Strips (Precision QID, XTRA)
Celecoxib (Celebrex)
Cyclosporine (Gengraf)
Darbpoetin (Aranesp)
Dorzolamide/Timolol (Cosopt)
Estradiol (Esclim)
Estropipate (Ortho Est)
Erythropoetin (Procrit)
Fexofenadine (Allegra)
Fluticasone (Flonase)
Hepatitis A Vaccine (Havrix, Vaqta)
Hepatitis A & B Vaccine (Twinrix)
Hepatitis B Vaccine (Recombivax HB, Engerix-B)
Interferon Beta (Betaseron)
Isometheptene/APAP/Dichloralphenazone (Midrin)
Lansoprazole (Prevacid)
Latanaprost (Xalatan)
Leuprolide (Lupron)
Loratadine (Claritin)
Methylphenidate (Concerta)
Methylphenidate (Metadate CD)
Nisoldipine (Sular)
Olanzapine (Zyprexa)
Pimecrolimus (Elidel)
Phenytoin (Bertek, Mylan generic)
Quetiapine (Seroquel)
Risedronate (Actonel)
Risperidone (Risperdal)
Rizatriptan (Maxalt)
Rofecoxib (Vioxx)
Rosiglitazone (Avandia)
Tolterodine (Detrol, Detrol LA)
Travoprost (Travatan)
Valdecoxib (Bextra)
Warfarin (Coumadin)

6. BCF CHANGES AND CLARIFICATIONS

A. *Bupropion SR* – CPT Jill Dacus (PEC) presented an analysis regarding the proposed addition of bupropion sustained release (SR) to the BCF, which was suggested by the Council at the November 2003 meeting while discussing the new once-daily formulation of bupropion (Wellbutrin XL). The FDA recently approved generic equivalents to GSK's Wellbutrin SR 100 mg; generics for the 150 mg strength are expected to follow in the near future.

Efficacy/Safety/Tolerability – Bupropion SR is a dopamine-reuptake blocker indicated for the treatment of depression and, as Zyban, for smoking cessation. The comparative efficacy of bupropion SR compared to other antidepressants on the BCF is unknown. Bupropion is useful for the treatment of depression in patients who have unacceptable adverse effects, such as sexual dysfunction or weight gain, with the selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). It is not considered a first line antidepressant due to an increased incidence of seizures (about 0.1% at 100-300 mg/day, increasing to 0.4% at the maximum recommended dose of 400 mg/day). There is no evidence that the once-daily formulation of bupropion (Wellbutrin XL) differs from twice-daily bupropion SR with regard to safety or efficacy; the FDA approved both formulations based on bioequivalency studies vs. the immediate release (3 times daily) formulation.

Other Factors – Bupropion SR 100 mg and 150 mg are on 80% (143/179) and 90% (161/179) of MTF formularies, respectively, with the less-widely used 200-mg strength on only 25% of MTF formularies. As of Dec 2003, MTF prescriptions for bupropion SR totaled about 18,000 per month (14,000 for Wellbutrin SR and 4,000 for Zyban). It is unknown how many Wellbutrin SR prescriptions were prescribed for smoking cessation rather than depression. There are about 100,000 MTF prescriptions for SSRIs (the most commonly prescribed antidepressant class) each month.

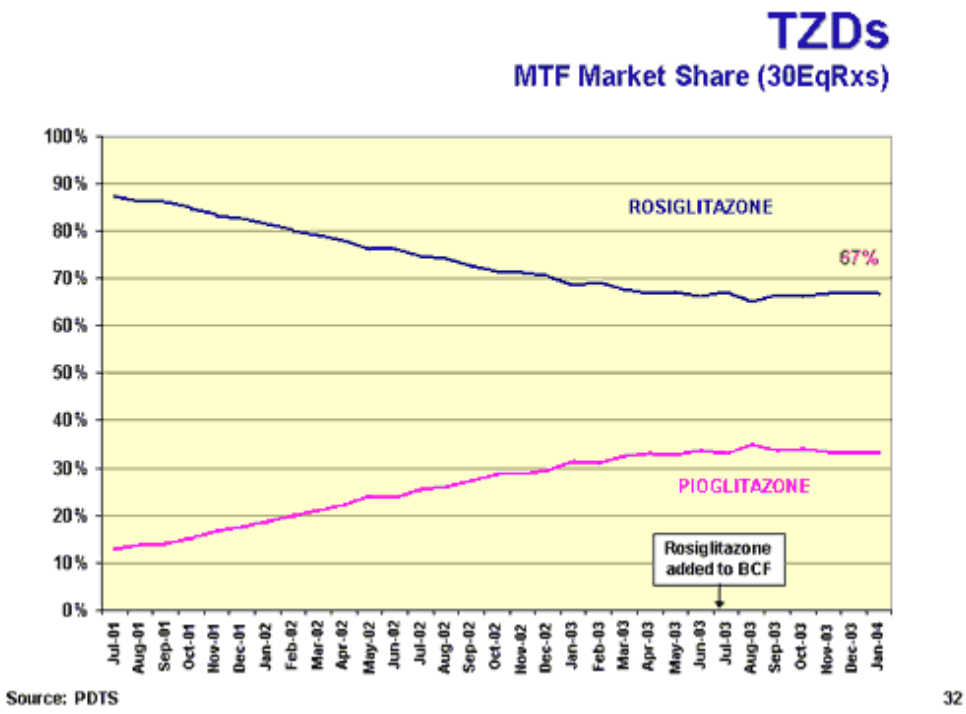
Cost – The current monthly cost for Wellbutrin SR is slightly higher than the newly introduced Wellbutrin XL ($60 vs. $58 per month, based on a typical daily dose of 300 mg). However, prices for bupropion SR should fall as generic competition increases.

The council voted unanimously to add bupropion SR 100 mg and 150 mg to the BCF based on its clinical utility in treating depressed patients who experience unacceptable adverse effects on SSRIs or TCAs, its broad representation on MTF formularies, and the increasing availability of generics. The BCF listing excludes Zyban. The presence of bupropion SR 100 mg and 150 mg on the BCF does not affect the ability of MTFs to place restrictions on the use of bupropion SR for smoking cessation if they so desire. For example, MTFs may institute and/or continue requirements that patients participate in counseling programs when bupropion SR is used for smoking cessation.

B. *Prednisolone Oral* – The BCF listing for prednisolone oral does not specify which dosage forms or strengths are on the BCF. MTF prescription data show minimal usage of prednisolone tablets. The most commonly utilized dosage form and strength is the 15 mg/5 mL syrup. The Council clarified the BCF listing for prednisolone oral to specify prednisolone 15 mg/5 mL syrup.

7. Thiazolidinediones (TZDs)

In June 2003, DoD and VA entered into an incentive agreement with GlaxoSmithKline to place rosiglitazone (Avandia), on the BCF as DoD's preferred thiazolidinedione (TZD) in exchange for a significant discount. The agreement requires that rosiglitazone maintain at least a 65% market share for DoD to achieve a substantial discount. Rosiglitazone's MTF market share had decreased from almost 90% in July 2001 to 67% in June 2003. Since the incentive agreement was implemented, rosiglitazone's market share has stabilized at 67%.



8. TRIPTANS

The zolmitriptan contract stipulates that zolmitriptan must be used for new patient starts on oral triptan therapy unless there is a medical necessity to use a different triptan. MTFs are permitted to have a second triptan on their local formulary for use by patients who have failed zolmitriptan. The contract does not mandate that patients who are already using other triptans be switched to zolmitriptan.

An analysis of prescription data for all MTFs in aggregate for December 2003 revealed that zolmitriptan was used for only 31% of new patient starts. The percentage of new patient starts for zolmitriptan varied significantly across MTFs, ranging from almost no use to as high as 81% (166/205) at Ft Bragg and 100% (22/22) at Pope AFB.

MTFs could achieve substantial cost avoidance by increasing the use of zolmitriptan for new patient starts. Zolmitriptan costs only $3.20 per dose regardless of strength. The price of other triptans depends on the formulary status at the individual MTF and any incentive agreements that may apply. However, prime vendor data for the first quarter of FY 04 show that the average cost per tablet for triptans other than zolmitriptan was $5.00. (Note: This

does not take into account the effect of rebates that an MTF may have obtained.) On average, MTFs could save $1.80 per dose by using zolmitriptan instead of other triptans.

9. CHOLINESTERASE INHIBITORS

CDR Briski presented an analysis of incentive agreements that have been proposed for donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon). Although the cholinesterase inhibitors have similar efficacy, donepezil is dosed once a day versus the twice daily dosing of galantamine and rivastigmine, requires fewer dosage titration steps to therapeutic dose, and appears to be better tolerated.

Donepezil accounted for 86% of the prescriptions filled at MTFs for cholinesterase inhibitors during the first quarter of FY 04. The results of a recently released clinical trial will probably help donepezil maintain or even increase its market share. The clinical trial compared donepezil in conjunction with memantine (an *N*-methyl-D-aspartate (NMDA) receptor antagonist) against donepezil plus placebo in moderate to severe Alzheimer's Disease. Patients treated with donepezil and memantine experienced significantly better outcomes than patients treated with donepezil and placebo on measures of cognition, activities of daily living, global outcome, and behavior.

Given the current and anticipated future usage trends for cholinesterase inhibitors and the pricing offered in the proposed incentive agreements, the analysis showed that DoD would obtain the greatest economic benefit by accepting the donepezil incentive agreement. The Council voted to add donepezil to the BCF and advise DSCP to accept the proposed incentive agreement for donepezil.

10. ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

A GAO protest caused the VA National Acquisition Center to withdraw the joint DoD/VA solicitation for an ARB in December 2003. The Council reviewed updated clinical information, usage data and cost data in order to formulate a DoD procurement strategy for the ARBs. The Council concluded that significant price reductions could be obtained by selecting one or more ARBs for addition to the BCF. The Council voted to have the PEC work with the Defense Supply Center Philadelphia (DCSP) to issue a BPA request for price quote for ARBs. The Council will consider the price quotes and clinical information about the ARBs to select at least one, but no more than two ARBs for addition to the BCF.

11. SECOND GENERATION ANTIHISTAMINES

The Council reviewed MTF usage and cost data for second generation antihistamines. MTF expenditures for second generation antihistamines are approaching $100 million annually. Although generic and brand name versions of loratadine are available at much lower prices than other second generation antihistamines, loratadine accounted for only 7.6% of the prescriptions for second generation antihistamines filled at MTF pharmacies during the first quarter of FY 04. Cetirizine (Zyrtec) and fexofenadine (Allegra) accounted for 47% and 45% of the prescriptions, respectively.

The Claritin brand of loratadine is available through a joint DoD/VA blanket purchase agreement for $0.38 per 10-mg tablet. Generic loratadine is available at prices as low as $0.12 per 10-mg tablet. Fexofenadine 180 mg costs $0.85 per tablet (incentive agreement

price for having fexofenadine on the BCF). The fexofenadine 180 mg price would increase to $1.42 per tablet if fexofenadine were not on the BCF. Cetirizine 10 mg costs $0.96 per tablet (Feb 2004 FSS price).

Some MTF pharmacy personnel have stated that the presence of fexofenadine on the BCF inhibits their ability to increase the use of loratadine at their MTFs. The Council considered a proposal to remove fexofenadine from the BCF. The Council was concerned that removal of fexofenadine from the BCF would not result in a large enough shift in market share to loratadine to make up for the negative financial impact of a fexofenadine price increase. The Council voted to keep fexofenadine on the BCF until there is evidence that MTFs are able to shift more usage to loratadine. The PEC will provide information to MTFs to assist them in this endeavor. The Council encourages MTFs to maximize the use of loratadine in lieu of other second generation antihistamines.

12. ADJOURNMENT

The meeting adjourned at 1400 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Tuesday, 20 April 2004. This meeting would normally be held in May, but the meeting will be held in April in order to accommodate training of Iraqi pharmacists in formulary management procedures. All agenda items should be submitted to the co-chairs no later than 19 March 2004.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **14 NOVEMBER 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 14 November 2003, at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
Col John R. Downs, MC	Air Force
Col Mark Nadeau, MC (For Col Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Dennis Alder	Coast Guard
Dr. Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Joe Canzolino (For Mike Valentino)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

CAPT Terrance Egland, MC	DoD P& T Committee Co-chair

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC, USN	Chief Medical Officer Representative, TMA
Howard Altschwager	Deputy General Counsel, TMA
LtCol Phil Samples, BSC, USAF	Air Force Pharmacy Consultant
COL Mike Heath, MS, USA	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
LTC Kent Maneval, MS, USA	Joint Readiness Clinical Advisory Board
Joe Torkildson, MD	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC, USN (via TC)	DoD Pharmacoeconomic Center
CDR Don Nichols, MC, USN	DoD Pharmacoeconomic Center
CDR Jill Pettit, MSC, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC, USAF (Via TC)	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
David Bretzke (via TC)	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
MAJ John Howe, MS, USA	Defense Supply Center Philadelphia
Gene Lakey	TriWest
William Hudson	Humana
Ron McDonald (via TC)	Sierra
Rance Hutchings, Pharm.D.	Uniformed Services Family Health Plans (USFHP)
LTC Gwendolyn Thompson, MS, USA	Pharmacy Practice Resident
CPT Jon Feagler, MS, USA	Pharmacy Practice Resident

3. **REVIEW MINUTES OF LAST MEETING** – The minutes from the last meeting were accepted as written.

4. **INTERIM/ADMINISTRATIVE DECISIONS** – None

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL William Davies, DoD Pharmacy Program Director, TMA, updated the Committee on the current status of the Uniform Formulary and the DoD P&T Committee Charter. The FY 2004 National Defense Authorization Act changes the membership of the DoD P&T Committee to include only government members. The DoD P&T Committee will therefore not be subject to the provisions of the Federal Advisory Committee Act.

6. BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 5 new drugs or formulations (see Appendix A).

7. PRIOR AUTHORIZATIONS (PAs)

A. *Growth Hormone* – Humatrope (somatropin [rDNA origin] for injection) was recently approved by the FDA as a treatment for non-growth hormone-dependent short stature, also known as Idiopathic Short Stature (ISS). This is the first FDA approval of a growth hormone product for ISS. Information regarding the use of growth hormone in pediatric growth disorders and potential costs in the treatment of ISS were presented by the PEC. Information regarding the use of somatropin in ISS considered by the FDA's Endocrinologic & Metabolic Drugs Advisory Committee as part of its review of Humatrope may be found on the FDA website at: http://www.fda.gov/ohrms/dockets/ac/cder03.html#EndocrinologicMetabolicDrugs (click on information from the 10 June 2003 meeting). For a brief overview, FDA summary slides from this advisory committee meeting are available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3957S1_03_FDA%20Slides.ppt.

Patients who have a growth hormone deficiency experience medical problems in addition to short stature (e.g. truncal adiposity, immature physical appearance, delayed puberty and decreased bone maturation), therefore it is medically necessary to provide growth hormone therapy to patients who have a growth hormone deficiency. Patients with ISS do not experience medical problems in addition to short stature; therefore it is not medically necessary to provide growth hormone therapy to patients with ISS. Since TRICARE will only pay for therapies that are medically necessary, TRICARE will not pay for growth hormone to treat ISS. The Council directed the PEC to develop a prior authorization for the use of growth hormone in adults and children. The prior authorization criteria will allow coverage for treatment of growth hormone deficiency and will deny coverage for treatment of ISS.

8. MAIL ORDER AND RETAIL NETWORK ISSUES

A. Carisoprodol Status on the TMOP Formulary – As of 9/19/2003, carisoprodol (Soma, generics) is classified as a Schedule IV controlled substance in the State of Arizona. Since the dispensing location for the TMOP is in Arizona, carisoprodol is subject to the same TMOP requirements as other Schedule IV controlled substances (limited to a 30-day supply and a maximum of 5 refills in a 6-month period).

B. Pravigard PAC Status on the TMOP Formulary – The price for Pravigard PAC (pravastatin and aspirin packaged together) recently decreased from $1.84-$2.70 to $0.74 - $1.49. Pravigard PAC is now the same price as brand name Pravachol. The Committee voted to add Pravigard PAC to the TMOP formulary.

C. Serevent Diskus Quantity Limits – The Committee revised quantity limits for the dry powder formulation of salmeterol (Serevent Diskus), which is twice as potent as the now discontinued metered dose inhaler formulation. The maximum recommended dose for Serevent Diskus is 1 inhalation twice daily. The new quantity limits are 1 inhaler (60 unit-dose blister packs) per 30 days at retail and 3 inhalers (180 unit-dose blister packs) per 90 days in the TMOP.

D. Zolmitriptan Nasal Spray Quantity Limits – The Committee approved new quantity limits for zolmitriptan nasal spray. The product is packaged 6 unit-doses per box. One or two unit-doses may be required per headache. Given the package size and package labeling indicating that the safety of treating more than 4 headaches with zolmitriptan in a 30 day period is not established, the Committee set quantity limits for zolmitriptan nasal spray at 36 units (6 boxes) per 90 days in the TMOP and 12 units (2 boxes) per 30 days in retail.

9. ADJOURNMENT – The meeting adjourned at 1200 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Thursday, 12 February 2004. All agenda items should be submitted to the co-chairs no later than 05 January 2004.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: DOD P&T COMMITTEE FORMULARY DECISIONS REGARDING NEWLY APPROVED DRUGS

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	TMOP Formulary status	TMOP and/or retail network formulary restrictions	BCF status
Bupropion HCl extended release tablets (Wellbutrin XL; GSK)	09 Sep 03. Indicated for the treatment of major depressive disorder in patients 18 years and older.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization:** None	Not added to the BCF **Similar BCF agents:** None. Several antidepressants are on the BCF, including 4 SSRIs, 4 TCAs, venlafaxine ER, and trazodone.
Bupropion HCl extended release tablets (Wellbutrin XL) are available in 150 mg and 300 mg formulations and are dosed once daily. Bupropion sustained release tablets are dosed BID and are available in 100, 150 and 200 mg tablets for depression (Wellbutrin SR), and 150 mg tablets for smoking cessation (Zyban). Generic versions are currently available only for bupropion immediate release tablets, which are available in 75 and 100 mg tablets and dosed TID. Generic versions of bupropion SR are expected to be available in the near future. Potential disadvantages related to the introduction of the Wellbutrin XL formulation include • Medication errors due to confusion about tablet strengths and differences in maximum dosages between the sustained and extended release products; • Lack of clinical trial information for the extended release product, which was approved based on bioequivalency data; • And potential misuse for smoking cessation. The potential advantage of the once-daily product for depression is largely based on convenience. Since the two peaks associated with bupropion SR are felt to be beneficial for smoking cessation, the once daily, extended release formulation is not expected to be as effective for this purpose as a twice-daily product. The extended release product is not FDA approved for smoking cessation.				
Ciprofloxacin 0.3% / dexamethasone 0.1% otic suspension (Ciprodex; Alcon)	18 Sep 03. Indicated for pediatric patients older than 6 months with acute otitis media with tympanostomy tubes, and for acute otitis externa in patients older than 6 months of age.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** There are no otic fluoroquinolones on the BCF. Neomycin / polymyxin B/ hydrocortisone otic suspension (Cortisporin, generics) is on the BCF.
Current otic preparations for treatment of ear infections include: • Ciprodex Otic (Alcon) – 0.3% ciprofloxacin/0.1% dexamethasone sterile suspension is approved in pediatric patients down to age 6 months with middle ear infections (otitis media) and tympanostomy tubes. (FSS $3.99/mL) • Cipro HC Otic (Alcon) – 0.2% ciprofloxacin/1% hydrocortisone non-sterile solution is approved for patients down to 1 year of age for acute otitis externa only. (FSS $3.99/mL) • Floxin Otic (Daiichi) and generic equivalents – 0.3% ofloxacin without a steroid component is a sterile solution approved for use in children down to 1 year of age for otitis externa, chronic suppurative otitis media, and acute otitis media in patients with tympanostomy tubes, and specifically for perforated tympanic membranes. (FSS $3.50/mL) • Cortisporin-TC Otic (Monarch) and generics – neomycin 3.3mg/polymyxin 3mg/hydrocortisone 1% is a non-sterile suspension approved for patients down to 2 years of age for otitis externa only and is not approved for use when the tympanic membrane is perforated. (FSS $0.58/mL) Currently, the BCF only contains one otic preparation for the treatment of ear infections, neomycin/polymyxin/hydrocortisone (Cortisporin Otic, generics), which is indicated for otitis externa only. Treatment options for otitis media will be reviewed at the February meeting to consider additional agents for BCF addition.				

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	TMOP Formulary status	TMOP and/or retail network formulary restrictions	BCF status
Levonorgestrel 0.15 mg / ethinyl estradiol 30 mcg tablets (Seasonale; Barr)	05 Sep 03: Prevention of pregnancy. Consists of 84 active tablets followed by 7 inert tablets (extended cycle use), reducing the number of yearly cycles from 12-13 to 4. The active ingredient/dosage strength of Seasonale is the same as Nordette, a monophasic oral contraceptive.	Added to the TMOP Formulary Note: In the Retail Network, 3 co-pays will be charged, as the product inherently contains a 90-day supply of medication.	**Quantity Limits** General rule applies. **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: There are several monophasic and triphasic oral contraceptives on the BCF, including LoEstrin, Lo-Ovral, and Triphasil.
Rosuvastatin tablets (Crestor; AstraZeneca)	14 Aug 03: Indicated as 1) an adjunct to diet to reduce TC, LDL, ApoB, non-HDL and TG and to increase HDL in primary hypercholesterolemia and mixed dyslipidemias; 2) as an adjunct to diet in patients with elevated TG levels; 3) to reduce LDL, TC, and Apo B in patients with homozygous familial hypercholesterolemia.	Not added to the TMOP Formulary. Medical necessity requirement must be met. (see comments)	**Quantity Limits** General rule applies to the Retail Network. **Prior Authorization** None	Not added to the BCF. The existing statin contract precludes BCF addition of rosuvastatin. (see comments) **Similar BCF agents**: Simvastatin and pravastatin.
Due to the existing DoD high potency statin contract awarded to simvastatin, rosuvastatin is reserved for patients who have a medical necessity to use a statin other than simvastatin. Examples of medical necessity include, but are not limited to: • Insufficient reduction of LDL-cholesterol after an adequate trial of simvastatin 80 mg • Patient is on long term therapy with a CYP-3A4 inhibitor or another medication known to interact with simvastatin • Patient experiences unacceptable side effects with simvastatin				
Vardenafil tablets (Levitra; Bayer / GSK)	19 Aug 03. Approved for the treatment of erectile dysfunction defined as the consistent or recurrent inability to attain and /or maintain a penile erection sufficient for sexual performance. Other drugs in the same class include sildenafil (Viagra), and tadalafil (Cialis), which was approved by the FDA on 21 Nov 03. Tadalafil (Cialis) will be reviewed by the Committee to determine TMOP status at the February 2004 meeting.	Not added to the TMOP Formulary	**Quantity Limits** Vardenafil quantity limits will be collectively 6 tablets per month with sildenafil and other oral impotency drugs. **Prior Authorization** Vardenafil will be subject to the same PA process as sildenafil (Viagra), consistent with the Health Affairs Sildenafil Policy	Not added to the BCF **Similar BCF agents:** There are no phosphodiesterase inhibitors on the BCF.
Notes about Vardenafil: Vardenafil is the second phosphodiesterase-5 (PDE-5) inhibitor to reach the market. It is similar to sildenafil in terms of pharmacokinetics (including onset of action), efficacy and safety. Concomitant use of either drug is contraindicated with nitrates due to the risk of hypotension. Concomitant use of vardenafil is contraindicated with alpha blockers; sildenafil labeling does not contain a contraindication for concomitant use with alpha blockers, although a warning against concomitant use of sildenafil at doses above 25 mg within 4 hours of taking an alpha blocker is listed under precautions. • **TMOP & Retail Network**: Vardenafil will have the same non-formulary status in the TMOP as sildenafil does. Both drugs will be available only if prior authorization criteria are met. Vardenafil will be subject to the same prior authorization process as sildenafil, consistent with guidelines in the Health Affairs Sildenafil Policy. A quantity limit of 18 tablets per 90 days will apply in the TMOP. A quality limit of 6 tablets per 30 days will apply in the retail network. The quantity limit will apply collectively to all oral PDE-5 inhibitors. This means that no more than 6 tablets per 30-day supply of any combination of these medications will be dispensed in the retail network and no more than 18 tablets per 90-day supply will be dispensed in the TMOP. • **BCF & MTF Formularies:** Guidelines listed in the Health Affairs Sildenafil Policy will also apply to vardenafil.			

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE NOVEMBER 2003 DOD P&T EXECUTIVE COUNCIL & THE DOD P&T COMMITTEE MEETINGS

1. **BCF CHANGES**

   A. *Additions to the BCF* - None

   B. Deletions, changes, clarifications or exclusions from the BCF

   1) Cyclobenzaprine – the BCF listing for cyclobenzaprine oral was clarified to exclude the 5 mg strength (high cost; only available as brand Flexeril).
   2) Zolmitriptan – the BCF listing for zolmitriptan does not include zolmitriptan nasal spray (high cost; not on contract)
   3) Lansoprazole – the BCF listing for lansoprazole was clarified to exclude the oral disintegrating tablets and delayed release suspension (high cost; capsules have FDA-approved alternative administration options for use in patients with difficulty swallowing).

2. **TMOP FORMULARY CHANGES**

   A. *Additions to the TMOP Formulary*

   1) Bupropion HCL extended release tablets (Wellbutrin XL)
   2) Ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension (Ciprodex)
   3) Levonorgestrel 0.15 mg/ethinyl estradiol 30 mcg tablets (Seasonale)
   4) Pravastatin/buffered aspirin (Pravigard PAC)

   B. Exclusions from the TMOP Formulary

   1) Vardenafil tablets (Levitra) – same non-formulary status in TMOP as sildenafil; available from the TMOP if prior authorization criteria are met. Quantity limits apply (see below)
   2) Rosuvastatin tablets (Crestor) – Due to existing DoD high potency statin contract awarded to simvastatin, rosuvastatin is available through the TMOP only for patients with evidence of medical necessity.

   C. Deletions, changes, or clarifications to the TMOP Formulary

   1) Carisoprodol (Soma, generics) – classified as a Schedule IV controlled substance in Arizona, where the TMOP dispensing facility is located. Subject to the same restrictions as a federally scheduled controlled substance (limited to a 30-day supply and a maximum of 5 refills in a 6-month period).

3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**

   A. Quantity limit for zolmitriptan (Zomig) nasal spray:

   - TMOP: 36 units (6 boxes) per 90 days
   - Retail: 12 units (2 boxes) per 30 days

   B. Quantity limits for salmeterol dry powder inhaler (Serevent Diskus):

   - TMOP: 3 inhalers per 90 days
   - Retail: 1 inhaler per 30 days

   C. Quantity limits for vardenafil tablets (Levitra) – will apply collectively to all oral PDE-5 inhibitors, including sildenafil (Viagra) and tadalafil (Cialis)

   - TMOP: 18 tablets per 90 days (any combination of oral PDE-5 inhibitors)
   - Retail: 6 tablets per 30 days (any combination of oral PDE-5 inhibitors)

4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION PROGRAM**

   A. Vardenafil will be subject to the same prior authorization process as sildenafil, consistent with guidelines in the Health Affairs Sildenafil Policy.

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MCCS-GPE **13 November 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council convened at 0800 hours on 13 November 2003 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
Col Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Dennis Alder	Coast Guard
Kathy Kelly (For Mike Valentino)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC	Chief Medical Officer Representative, TMA
COL Mike Heath, MS	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
LtCol Phil Samples, BSC (For Col Ardis Meier, BSC)	Air Force Pharmacy Consultant
MAJ John Howe, BSC	Defense Supply Center Philadelphia
LTC Kent Maneval, USA, MS	Joint Readiness Clinical Advisory Board
CAPT Don Nichols, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR Jill Pettit, MSC	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC (via TC)	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC (via TC)	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC	DoD Pharmacoeconomic Center
Joe Torkildson, MD	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke (via TC)	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
MAJ Barbara Hoeben, BSC	UT College of Pharmacy Master's Program
SFC Agustin Serrano	DoD Pharmacoeconomic Center

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

None

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARDS, RENEWALS AND TERMINATIONS

A. The next option years were exercised for the following contracts: human insulin, and cyclobenzaprine.

B. Option years to be exercised over the next two months include the following contracts: albuterol, colchicine, permethrin, and tretinoin cream.

C. Option years not exercised due to current lower FSS prices than the contract price: rifampin, sucralfate, and salsalate.

D. DSCP signed an incentive agreement with Merck for alendronate (Fosamax) that became effective 1 October 2003. The agreement stipulates that alendronate will be the only bisphosphonate on the BCF. The class remains open on the BCF, so MTFs may have additional bisphosphonates on their formularies. The incentive agreement contains a

confidentiality clause that prohibits disclosure of the specific terms and conditions of the agreement, but it substantially reduces the price of alendronate. Estimated cost avoidance for DoD is $690,000 for the single month of October 2003.

6. PROCUREMENT INITIATIVES

A. *Oral Fluoroquinolones* – The Oral Fluoroquinolone Solicitation was posted on October 22, 2003. The solicitation offers the addition of a single oral fluoroquinolone to the Basic Core Formulary (BCF) as a workhorse agent to use in the treatment of community acquired pneumonia (CAP) and sinusitis. The solicitation closed on November 11, 2003. The award is pending.

B. *Angiotensin Receptor Blockers (ARBs)* – The ARB Solicitation was released in August 2003. The solicitation has been protested. DoD/VA is addressing the protest.

C. *Cholinesterase Inhibitors* – Two companies have offered BPAs on cholinesterase inhibitors. The Council asked the PEC to analyze the proposed BPAs and make recommendations at the next meeting.

D. *Brimonidine 0.2% Ophthalmic Solution* – The current BCF listing for brimonidine ophthalmic solution specifies the 0.15% formulation (Alphagan P). The Council placed Alphagan P on the BCF in Feb 2002 due to the planned phase-out of the 0.2% formulation by the manufacturer. The difference between the formulations is the preservative used; the 0.15% formulation (Alphagan P) contains a purite preservative, while the 0.2% formulation contains a benzylalkonium (BAK) preservative. Generic equivalents of the 0.2% formulation are now available. As part of the FDA review of generic brimonidine, the FDA determined that differences in intra-ocular pressure (IOP) lowering and adverse events between the two formulations were not clinically significant. Since generic versions of brimonidine 0.2% cost considerably less than brimonidine 0.15% (Alphagan P), the Council expressed interest in a potential sole source contract to compete generic brimonidine products for BCF addition. This issue will be reviewed at the next meeting.

7. REVIEW OF EXISTING PROCUREMENT INITIATIVES

A. *LHRH Agonists* – Goserelin Acetate Implant (AstraZeneca) was awarded a contract, effective 17 Feb 03, as the sole LHRH agonist on the BCF and VA National Formulary (VANF) for the treatment of prostate cancer. DoD has cost avoided approximately $213,000 since the contract was implemented. Goserelin acetate implants accounted for the following percentages (based on "treatment month equivalents") of LHRH agonist products purchased by MTFs during September 2003:

- DoD: 43%
- AF: 34%
- Army: 40%
- Navy: 59%

The contract reduced the price of goserelin acetate implants by 32%, which would have yielded a potential cost avoidance of $579,564 if goserelin acetate implants had accounted for 100% of the purchases. Since this class of drugs has indications other than

prostate cancer, some utilization of competing products is expected. Goserelin's market share is increasing slightly.

B. *Statins* – Simvastatin (Merck and Co) was awarded a joint VA/DoD contract, effective 1 May 03, as the sole high-potency statin on the BCF and VANF for the treatment of hyperlipidemia. MTFs may also have lovastatin and either pravastatin or fluvastatin on their formularies. DoD cost avoided approximately $31,652,000 during FY 03 within this class of drugs. The cost avoidance includes the old DoD contract and the first 3 months of the joint VA/DoD contract. Simvastatin accounted for the following percentages (based on tablets/capsules) of statins purchased by MTFs during September 2003:
   - DoD: 93.4%
   - AF: 95.6%
   - Army: 92.8%
   - Navy: 90.7%

   On average, simvastatin prices are 20% less than they were under the initial DoD statin contract and 45% less than they were prior to the initial contract.

C. *Triptans* – Zolmitriptan (AstraZeneca) was awarded a contract, effective 11 July 03, as the sole 5HT1 agonist on the BCF. MTFs may have no more than one 5HT1 agonist in addition to zolmitriptan on their formularies. DoD cost avoided $701,843 during the first two months of the contract. Zolmitriptan accounted for the following percentages (based on tablets) of triptans purchased by MTFs during September 2003:
   - DoD: 12%
   - AF: 12%
   - Army: 13%
   - Navy: 11%

   Zomitriptan prices are 50% less than they were before the contract. Given the large price reduction, MTFs can increase their cost avoidance by maximizing the use of zolmitriptan in lieu of other 5HT1 agonists.

D. *Nasal Steroids* – An incentive agreement for fluticasone (Flonase) nasal spray became effective 1 January 2003 and stipulated that fluticasone would be the sole aqueous nasal corticosteroid on the BCF. The class remains open on the BCF, so MTFs may have additional nasal corticosteroids on their formularies. The incentive agreement did not reduce the price of fluticasone, but it prevented an increase in price that would have occurred if MTFs had to purchase the product at the Federal Supply Schedule (FSS) price. Fluticasone nasal spray accounted for 87% of the nasal corticosteroid prescription fills at MTF pharmacies in September 2003.

E. *Proton Pump Inhibitors (PPIs)* – Rabeprazole (Aciphex) and lansoprazole (Prevacid) are the two PPIs on the BCF in accordance with the terms of incentive agreements that took effect 1 April 2003. The class remains open on the BCF, so MTFs may have additional PPIs on their formularies. Rabeprazole and lansoprazole accounted for approximately 75% and 17% respectively of PPI prescription fills at MTFs in September 2003. The weighted average cost per dose for PPIs was $0.80 in September 2003, compared to $0.40 per dose for most of calendar year 2002. The increase in cost is primarily due to a large price increase for rabeprazole. Prices for PPIs may decrease when price competition increases for generic omeprazole.

F. *Thiazolidinediones (TZDs, "Glitazones")* – Rosiglitazone (Avandia) is the only TZD on the BCF in accordance with the terms of an incentive agreement that took effect in July 2003. The class remains open on the BCF, so MTFs may have additional TZDs on their formularies. Rosiglitazone accounted for 66% of the 30-day equivalent prescriptions for TZDs at MTFs in September 2003. DoD cost avoidance for the first two months of the agreement is approximately $360,000.

G. *Second-Generation Antihistamines* – Loratadine is available to MTFs through an incentive agreement at less than half the price of other second-generation antihistamines, but loratadine accounted for only 6% of 30-day equivalent prescriptions for second-generation antihistamines at MTFs as of October 2003. The weighted average cost per dose for second-generation antihistamines at MTFs increased from $0.70 in March 2003 to $0.86 in August 2003. The Council encourages MTFs to maximize the use of loratadine (consistent with patients' clinical needs) in lieu of other second-generation antihistamines.

H. *Other Blanket Purchase Agreements (BPAs)* – The Council reviewed utilization data for ophthalmic prostaglandins, atypical antipsychotics, topical immunomodulators (TIMs), and tolterodine extended release. An estimate of the cost avoidance realized will be reported at the next meeting.

8. PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS FOR ERECTILE DYSFUNCTION

In light of the recent FDA approval of a second PDE-5 inhibitor—vardenafil (Levitra)—the Health Affairs Director of Clinical Program Integration asked the DoD P&T Executive Council to review Health Affairs Policy 98-040, "Practice Guidelines for the Evaluation of Patients Requesting Sildenafil, (Viagra), for the Treatment of Male Impotence" and recommend whether the policy should be continued, modified, or rescinded. The policy mandates that sildenafil will be:

- non-formulary throughout the Military Health System (MHS)
- provided to patients only through a special order or prior authorization process
- subject to a quantity limit of six tablets per month

Based on information provided by the PEC, the Council identified the following concerns with Health Affairs Policy 98-040:

- The mandatory non-formulary status and requirement to special order or prior authorize prescriptions for sildenafil are an administrative hassle for patients, prescribers and pharmacies.
- The mandatory non-formulary status and requirement to special order or prior authorize sildenafil prescriptions inhibits the ability of MTF pharmacies to "recapture" prescription workload from the more expensive retail point of service.
- The mandatory non-formulary status precludes DoD from using formulary or procurement strategies to reduce the acquisition cost of PDE-5 inhibitors.
- One of the goals of the prior authorization process in the TMOP and retail network pharmacies is to identify patients who have psychogenic versus organic erectile

dysfunction because TRICARE does not cover the treatment of psychogenic erectile dysfunction. The prior authorization process is not meeting this goal because providers typically do not attempt to differentiate psychogenic erectile dysfunction from organic erectile dysfunction or mixed psychogenic/organic erectile dysfunction. The diagnostic tests required to confirm the diagnosis of organic erectile dysfunction are generally considered to be excessively expensive, invasive and pose unnecessary risk to the patient.

- The special order or prior authorization process is probably increasing the cost of providing erectile dysfunction therapy. In the TMOP, 27% of the prior authorization requests would have to be denied in order for DoD to break even on the cost of processing the prior authorizations versus the drug costs avoided by denying prescriptions. Over 95% of PA requests are approved in the TMOP. Unless the "sentinel effect" of the prior authorization process is large, DoD is losing money on the prior authorization process. [Note: The "sentinel effect" occurs when the requirement to obtain prior authorization causes a provider to refrain from writing a prescription for the drug.]

The Council voted to recommend that Health Affairs rescind HA Policy 98-040 and allow the DoD P&T Committee to manage the use of PDE-5 inhibitors as follows:

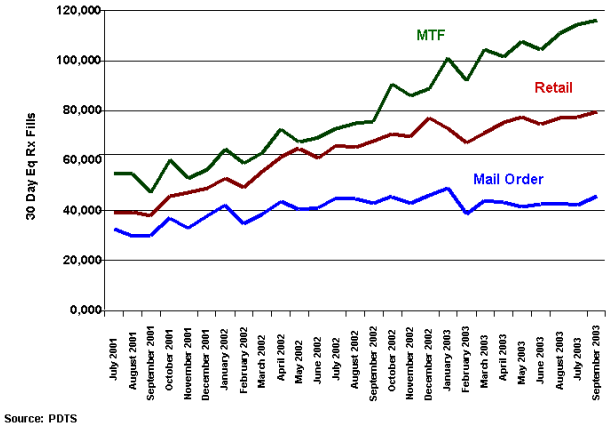
- Retain the quantity limit of six tablets per month.
- Discontinue the requirement for special order or prior authorization.
- Continue to utilize the prospective drug utilization review capabilities of CHCS and PDTS for safety monitoring.
- Consider formulary or contracting strategies to reduce the acquisition cost of PDE-5 inhibitors.

Although Health Affairs Policy 98-040 refers only to sildenafil, all PDE-5 inhibitors will be subject to the provisions of HA Policy 98-040 until Health Affairs rescinds or revises the policy.

9. DRUG/DRUG CLASS EVALUATIONS

A. Cox II Inhibitors – The Council reviewed the utilization and costs of non-steroidal anti-inflammatory drugs (NSAIDs), including the COX-2 selective NSAIDs ("COX-2 inhibitors"), in the three DoD pharmacy points of service. Utilization of COX-2 inhibitors is still increasing in MTFs and the retail network (see Figure 1 below).

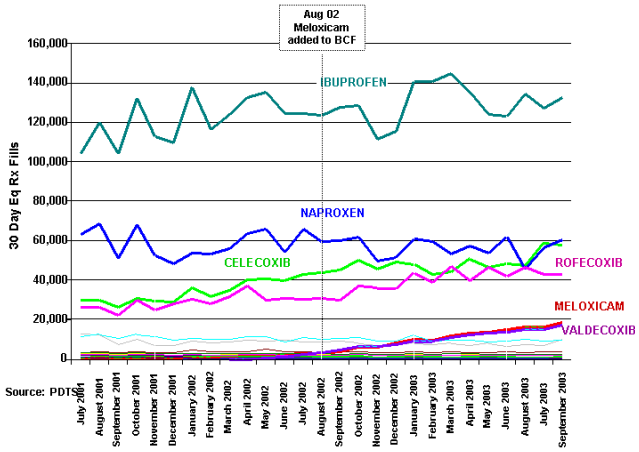
Figure 1: 30-day Equivalent Rxs for COX-2 Selective NSAIDs (Celecoxib, Rofecoxib, Valdecoxib) by Point of Service, Jul 01-Sep 03



Source: PDTS

Utilization of meloxicam (Mobic; Boehringer-Ingelheim), which was added to the BCF in August 2002 as a "relatively" COX-2 selective NSAID, has increased markedly in MTFs, closely tracking utilization of the most recently approved COX-2 inhibitor, valdecoxib (Bextra; Pfizer) (see Figure 2, below). Utilization of non-selective NSAIDs (e.g., ibuprofen, naproxen) remains essentially constant.

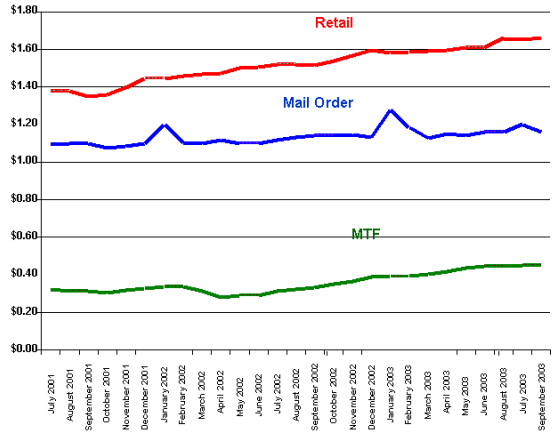
Figure 2: MTF 30-day Equivalent Rxs for NSAIDs, Jul 01 – Sep 03



Source: PDTS

As of Sep 03, monthly costs for NSAID therapy were about $8M in the retail network, $7.5M for MTFs, and $2.5 million in mail order. The cost per unit for NSAID therapy has increased in all points of service since Jul 01 (see Figure 3, below), primarily due to increasing use of COX-2 selective NSAIDs.

Figure 3: NSAID Cost per Unit by Point of Service, Jul 01 – Sep 03



Source: PDTS

Staff members from the PEC and the VA PBM are currently working on a joint DoD/VA NSAID review to support a potential joint procurement initiative for COX-2 selective and/or relatively COX-2 selective NSAIDs.

10. REQUESTS FOR BCF CHANGES

A. Cyclobenzaprine (Flexeril) 5 mg

Cyclobenzaprine tablets are on the BCF. The contract price is $0.02 per 10 mg tablet. The FDA approved a new 5 mg strength of the brand name Flexeril in February 2003. The FSS price of the branded Flexeril 5 mg tablet is $0.54. Due to the high cost of the 5 mg strength, the Council clarified the BCF listing for cyclobenzaprine to exclude Flexeril 5 mg tablets.

B. Zolmitriptan Nasal Spray

Zolmitriptan tablets are on the BCF. Zolmitriptan nasal spray was approved in October 2003. Zolmitriptan nasal spray is not included in the current triptan contract. The FSS price of zolmitriptan 5 mg nasal spray is $15.48/dose ($92.88 per box of 6 spray devices), which is much higher than the contract price of $3.20/2.5 mg or 5 mg tablet. Due to the high cost, the Council agreed that zolmitriptan nasal spray would not be included on the BCF.

C. Lansoprazole Oral Disintegrating Tablets and Delayed Release Suspension

Lansoprazole capsules (Prevacid) are currently on the BCF with an incentive agreement price of $0.65/capsule. Two new formulations of lansoprazole are available, a delayed release oral suspension and an orally disintegrating tablet. The FSS prices for the suspension are $2.00/15 mg packet and $2.28/30 mg packet. The orally disintegrating tablets are $2.80/15 mg tablet and $2.85/30 mg tablet. Although these new formulations could potentially improve ease of use in pediatric and geriatric populations, the existing

capsules are approved for pediatric use in patients 1 year of age or older. They can be opened and sprinkled on soft foods or mixed with liquids and administered enterally. The delayed release suspension comes in packets that must be mixed with water and used immediately upon reconstitution. Since the suspension thickens quickly they should not be used enterally. Due to the high cost and the existence of FDA approved alternative administration options for lansoprazole capsules, the Council clarified the BCF listing for lansoprazole to exclude the oral disintegrating tablets and delayed release suspension.

D. Transdermal Scopolamine Patch

CPT Jill Dacus (PEC) presented a request from a nurse anesthetist for the addition of transdermal scopolamine patch to the BCF. The requestor's rationale was based on two considerations:

1. Transdermal scopolamine would be more cost effective than the majority of serotonin antagonists (e.g., dolasetron, granisetron, ondansetron) for prophylaxis of post-operative nausea and vomiting (PONV).

2. The potential exists for increased use of transdermal scopolamine in ambulatory surgery patients now that droperidol, formerly the most popular antiemetic for PONV, has a black box warning for QT prolongation.

Efficacy/Safety/Tolerability – Transdermal scopolamine has been proven efficacious in the prophylaxis of PONV. In a meta-analysis of 23 trials with scopolamine (N = 979) and placebo (N = 984), the relative risk for vomiting was 0.69 (95% CI 0.58-0.82), with an absolute risk reduction of 17%, and a number needed to treat (NNT) of 5.9. However, the American Society of Anesthesia Task Force on Postanesthetic Care's 2002 Practice Guidelines do not recommend scopolamine patches as first line prophylaxis, stating that the evidence for its use is less robust than for other anti-emetic agents. Scopolamine is contraindicated in children and patients with narrow angle glaucoma. Caution is advised in the elderly due to increased sensitivity to scopolamine's CNS effects, such as confusion, agitation, and hallucinations. The most common side effect is dry mouth, which occurs in 2 out of 3 patients. Administration of scopolamine for prophylaxis of PONV following ambulatory surgery is somewhat cumbersome because the patient would have to obtain the patch and apply it the evening before surgery.

Cost – The MTF average cost per dose for scopolamine is generally lower than the cost for serotonin antagonists, but is higher than the cost for other antiemetics used for PONV (e.g. promethazine). MTFs currently spend about $250K per month on serotonin antagonists, compared to $50,000 per month or less for other perioperative antiemetics.

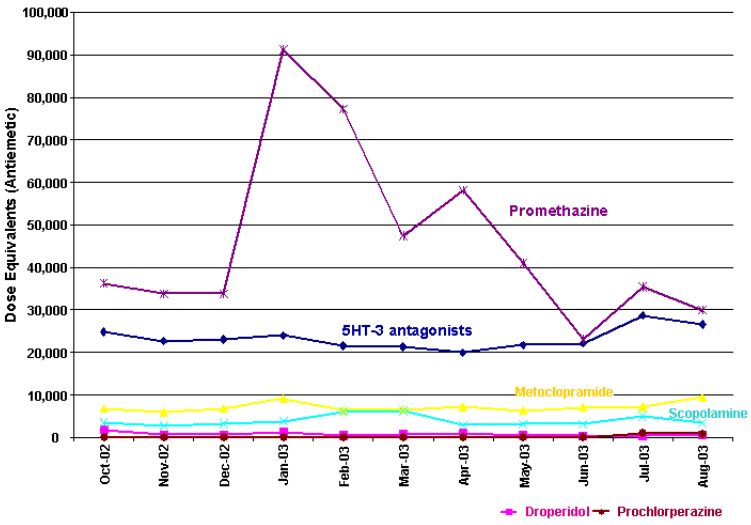
Table 1: Prime Vendor Acquisition Costs (Mean Cost per Dose, Oct 02 – Aug 03)

Antiemetic	Dosage & Route	Mean Cost per Dose
Scopolamine	1.5 mg/24 h TD placed night before surgery	$6.98*
Droperidol	1.25mg IM/IV prior to surgery	$1.63
Prochlorperazine	5-10mg IM/IV 1-2hr before surgery	$3.76-7.56
Promethazine	25-50 mg IM/IV 1-2hr before surgery	$0.05-0.16
Dolasetron	100mg PO, 12.5mg IV, within 2h start of surgery	$5.01, $24.46
Granisetron	1mg IV 30sec before anesthesia induction	$58.24
Ondansetron	16mg PO, 16mg solution PO, 4mg IV, 1hr before anesthesia	$32.46, $38.00, $11.86
Metoclopramide	10-20mg IM injection near end of surgery	$1.92-3.84

*Note: 87% of MTF purchases were for scopolamine patches in boxes of 4 at a cost of $8.59/patch; 23% of purchases were for boxes of 24 at a cost of $2.68/patch.

Utilization –MTFs purchase more dose equivalents of serotonin antagonists, promethazine and metoclopramide than they do scopolamine transdermal patches. However, purchases of scopolamine patches are higher (in terms of dose equivalents) than droperidol, which has a new black box warning, or prochlorperazine, which has not been widely available due to a national drug shortage. Table 4 shows total purchases of all of these agents, which may also be used for indications other than prophylaxis of PONV.

Figure 4: MTF Purchases of Injectable and Transdermal Antiemetics By Dose Equivalents (Oct 02 – Aug 03)



Conclusion: The Council voted unanimously not to add transdermal scopolamine to the BCF based on its high cost, low utilization, cumbersome administration requirements for PONV, and the American Society of Anesthesia Task Force on Postanesthetic Care recommendations.

E. Extended Release Morphine

Due to a lack of raw materials (opium poppy), there is a shortage of 15 mg and 30 mg strengths of MS Contin and generic morphine sulfate extended release products other than Mallincrodt's product. Mallincrodt anticipates no shortages of any strength since it is the principal supplier for all manufacturers of morphine sulfate products. The current BCF listing is for MS Contin or its generic equivalent in strengths of 15, 30, and 60 mg. Mallincrodt has an FDA-approved generic morphine sulfate extended release product that is A-B rated to MS Contin. FSS pricing for Mallinckrodt's product is less than the current FSS price for MS Contin. MTFs should be aware that the generic Mallincrodt product is currently a stable source of supply for oral morphine sulfate extended release.

11. ADJOURNMENT

The meeting adjourned at 1400 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Wednesday, 11 February 2004. All agenda items should be submitted to the co-chairs no later than 05 January 2004.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **6 AUGUST 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 6 August 2003, at the TRICARE Management Activity (TMA), Falls Church, VA.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
COL Mike Heath, MS (For MAJ Travis Watson, MS)	Army
LtCol Kimberly May, MC (For Col John R. Downs, MC)	Air Force
Col Bill Sykora, MC	Air Force
LtCol Phil Samples, BSC (For LtCol George Jones, BSC)	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Charles Bruner	Coast Guard
Rance Hutchings, Pharm.D. (For Dr. Trevor Rabie)	Uniformed Services Family Health Plans (USFHP)
Francine Goodman (For Mike Valentino)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Col Ardis Meier, BSC	Air Force Pharmacy Consultant
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
LtCol Dave Bennett, USAF, BSC (Via VTC)	DoD Pharmacoeconomic Center
LtCol Barb Roach, USAF, MC (Via VTC)	DoD Pharmacoeconomic Center
CPT Jill Dacus, USA, MC (Via VTC)	DoD Pharmacoeconomic Center
David Bretzke (via VTC)	DoD Pharmacoeconomic Center
Eugene Moore (via VTC)	DoD Pharmacoeconomic Center
Angela Allerman (via VTC)	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
MAJ John Howe, MS	Defense Supply Center Philadelphia
Gene Lakey	TriWest
William Hudson	Humana
Kelly Lenhart	Humana

3. **REVIEW MINUTES OF LAST MEETING/ADMINISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **INTERIM DECISIONS**

An interim "email" DoD Executive Council Meeting resulted in the following BCF and TMOP changes:

- Latanoprost (Xalatan) was added to the BCF
- Rosiglitazone (Avandia) was added to the BCF
- Rosiglitazone/metformin (Avandamet) was added to the BCF
- Serevent MDI was removed from the BCF due to market withdrawal. Serevent DPI will be the remaining salmeterol on the BCF.
- Zolmitriptan oral tablets (Zomig) were added to the BCF
- Sumatriptan oral tablets (Imitrex) were removed from the BCF
- Gefitinib (Iressa) was added to the TMOP with quantity limits
- Lovastatin extended release (Altocor) was removed from the TMOP

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL William Davies, DoD Pharmacy Program Director, TMA, stated that the current plan is to implement the Uniform Formulary in conjunction with the TRICARE Retail Pharmacy (TRRx) contract. The TRRx contract is scheduled for implementation in Spring 2004.

6. **BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES** – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 11 new drugs or formulations (see Appendix A). The PEC also presented brief information on eleven additional new drugs or formulations not requiring action by the Committee (see Appendix B). The Committee agreed that no further review was required.

7. **MAIL ORDER AND RETAIL NETWORK ISSUES**

   A. *TMOP* – Lisa LeGette from Express Scripts provided a TMOP update to the Committee.

   B. *TMOP Prior Authorizations (PAs)* – Shana Trice provided an update on TMOP PAs.

   C. *Change to TMOP PA for Etanercept* - Etanercept (Enbrel) was recently approved for ankylosing spondylitis, a chronic disease involving inflammation of the sacroiliac, intervertebral, and costovertebral joints. Ankylosing spondylitis affects approximately 350,000 patients in the United States. The Committee unanimously added treatment of ankylosing spondylitis to the PA criteria for etanercept. TMOP PA criteria and forms are available on the PEC website at www.pec.ha.osd.mil/TMOP/TMOPhome.htm#2c-PA.

8. **CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS** – Enfuvirtide (Fuzeon) is approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Roche Laboratories and Trimeris have contracted the distribution of Fuzeon to the specialty pharmacy operator Chronimed. Fuzeon is available through the TRICARE retail pharmacy benefit through the Fuzeon Progressive Distribution Program established by Chronimed and as described on their website, www.fuzeon.com.

   DoD has made arrangements with Chronimed to make Fuzeon available for MTF pharmacies to purchase and dispense to their patients. The procedure for MTF pharmacies to purchase Fuzeon with their department credit card is outlined on the DoD Fuzeon Procurement Form. The DoD Fuzeon Procurement Form is available for download at the PEC website, http://www.pec.ha.osd.mil/Controlled_Distribution_Drugs.htm, or in the File Library of RxNET, www.dodrxnet.org. Purchases through this mechanism will be billed at federal pricing. Commercial pricing applies to prescriptions filled through the TRICARE retail pharmacy benefit.

   Air Force pharmacies can obtain Fuzeon through the Air Force's High Dollar Program, which is managed out of Wright-Patterson Air Force Base. Air Force facilities wanting to use the High Dollar Program should complete the request forms provided by Wright-Patterson and not the DoD Fuzeon Procurement form described here.

   Questions about the DoD Fuzeon Procurement Form can be directed to David Bretzke or CDR Ted Briski of the DoD Pharmacoeconomic Center at (210) 295-1271.

9. ADJOURNMENT – The meeting adjourned at 1100 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Friday, 14 November 2003. All agenda items should be submitted to the co-chairs no later than 06 October 2003.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: DOD P&T COMMITTEE FORMULARY DECISIONS REGARDING NEWLY APPROVED DRUGS

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	TMOP Formulary status	TMOP and/or retail network formulary restrictions	BCF status
Moxifloxacin ophthalmic solution 0.5% (Vigamox; Allergan)	16 Apr 03: Fourth generation quinolone ophthalmic antibiotic indicated for treating bacterial conjunctivitis caused by susceptible strains of aerobic gram positive and aerobic gram negative organisms and Chlamydia.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization:** None	Not added to the BCF **Similar BCF agents:** None
Oxybutynin transdermal system (Oxytrol; Watson)	10 Mar 03: First transdermal formulation of oxybutynin for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. Applied every 3-4 days (twice weekly). The product is packaged in 1 carton containing 8 patches, a 30-day supply.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Oxybutynin oral (immediate release tablets) and tolterodine extended release capsules are on the BCF
Influenza intranasal vaccine (FluMist; Medimmune/Wyeth)	17 Jun 03: First nasally administered live influenza virus vaccine. Approved for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children ages 5-17 and healthy adults ages 18-49. FluMist is not to be administered to asthmatics, immunocompromised patients, or patients taking drugs which compromise the immune system (chemo agents, high dose steroids, etc).	Not added to the TMOP Formulary The product is not intended for self-administration and must remain frozen prior to use.	**Quantity Limits** N/A **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None
Omalizumab injection (Xolair; Genentech/Novartis)	20 Jun 03: First injectable monoclonal antibody that targets the IgE antibody. Approved for treatment of patients 12 years of age and older with moderate to severe allergy-related asthma that is inadequately controlled with inhaled steroid treatments. Eligible patients must have a positive skin test or *in vitro* reactivity to perennial allergies to confirm the diagnosis of allergy-related asthma.	Not added to the TMOP Formulary	**Quantity Limits** N/A **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None

Note about Omalizumab: Omalizumab injection will not be available from the TMOP due to the following reasons:

1) The product is not labeled or packaged for patient self-administration. No patient instruction information is enclosed in the package insert.
2) The risk of anaphylaxis and lack of clinical experience with omalizumab does not support its use outside of a controlled environment.
3) Reconstitution and administration requirements make patient preparation difficult. (Omalizumab is a lyophilized powder that takes 15-20 minutes to dissolve. Subcutaneous administration of the viscous liquid takes 5-10 seconds, and multiple injection sites may be needed due to the injection volume.)
4) Commercial distribution is limited to a specialty pharmacy network that supplies medications to physicians' offices.

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	TMOP Formulary status	TMOP and/or retail network formulary restrictions	BCF status
Pravastatin/ buffered aspirin tablets (Pravigard PAC; BMS)	24 Jun 03: This product is not a single tablet formulation, but simply two tablets (pravastatin and buffered aspirin) packaged side-by-side in the same blister pack. Six dosage strengths are available (3 dosages of pravastatin, 20, 40 and 80 mg; with 2 aspirin dosages 81 mg and 325 mg). The product requires a prescription. Indications are to reduce the occurrence of cardiovascular events, including death, MI or stroke in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease. Pravigard PAC is only indicated for secondary prevention of cardiovascular disease; pravastatin is indicated for both primary and secondary prevention.	Not added to the TMOP Formulary	**Quantity Limits** N/A **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Simvastatin
Notes about Pravigard PAC: • **TMOP**: Pravigard PAC was not added to the TMOP Formulary as it costs a lot more than pravastatin and aspirin that are not packaged together and provides no additional clinical benefit. (Pravigard PAC FSS prices: 20 mg + ASA: $1.84/day; 40 mg +ASA or 80 mg + ASA $2.70/day. Pravastatin FSS prices: 20 mg: $0.75/day; 40 mg: $1.30/day; 80 mg: $1.49/day. Aspirin: Less than $0.01/day.) Pravastatin is available from the TMOP, which will meet the clinical needs of patients with prescriptions for Pravigard PAC. • **BCF & MTF Formularies:** Pravigard PAC was not added to the BCF. The statin contract allows MTFs to have either pravastatin or fluvastatin on their formularies, but not both. MTFs cannot add Pravigard PAC to their local formulary if fluvastatin is on their formulary. MTFs may add Pravigard PAC to their formulary if pravastatin is on their formulary, but MTFs are advised not to add Pravigard PAC to their formulary because it costs too much			
Testosterone buccal system mucoadhesive (Striant; Columbia)	Jun 03: Buccal testosterone mucoadhesive is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Schedule III product.	Added to the TMOP, consistent with inclusion of other non-injectable testosterone products	**Quantity Limits** TMOP: 3 cartons per 90 days Note: although there is a 30-day supply limit on most controlled substances dispensed by the TMOP, other topical androgen replacement products have a 90-day supply limit in the TMOP. Retail: 1 carton per 30 days **Prior Authorization** None	Not added to the BCF. **Similar BCF agents:** None.
Note about Testosterone Buccal System Mucoadhesive: This product is supplied in a blister card of 10 buccal systems, with a total of 6 blister cards (60 buccal systems) in each carton. Anticipated retail cost for one month is $149.35 /60 systems= $4.97/day (need 2 systems/day). As of July 15, there was no FSS listing for this formulation.				

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Conjugated estrogen / medroxyprogesterone acetate (Prempro 0.3/1.5; Wyeth)	Jun 03: Lower-dose formulation of Prempro contains 0.45 mg of estrogen, and 1.5 mg of progestin (existing Prempro doses include 0.625 / 2.5 mg, and 0.45 mg / 1.5 mg which was approved in April 2003). Approved for both menopausal vasomotor symptoms and osteoporosis.	Added to the TMOP (line extension)	**Quantity Limits** N/A **Prior Authorization** None	BCF listing for conjugated estrogens / medroxy-progesterone oral (Prempro) will include the 0.3/1.5 mg strength
Conjugated estrogen 0.45 mg (Premarin; Wyeth)	Jun 03: Lower-dose formulation of conjugated estrogens approved for both menopausal vasomotor symptoms and osteoporosis.	Added to the TMOP (line extension)	**Quantity Limits** N/A **Prior Authorization** None	BCF listing for conjugated estrogens will include the 0.45 mg strength.
Clonazepam orally disintegrating tablets (Klonopin Wafers; Solvay)	May 03: Rapidly dissolving formulation of clonazepam, available in 0.125, 0.25, 0.5, 1 and 2 mg sizes. There is no FSS price yet for the new formulation, but it is anticipated to be considerably more costly than generic clonazepam tablets, which cost approximately $0.05 per tab. The Committee agreed that the clinical benefit was unlikely to be sufficient to justify the increased cost for the rapidly dissolving formulation.	Added to the TMOP (line extension)	**Quantity Limits** N/A **Prior Authorization** None	The BCF listing for clonazepam 0.5 mg was clarified to exclude clonazepam orally disintegrating tablets.
Risperidone orally disintegrating tablets (Risperdal Redi-tabs; J&J)	May 03: Rapidly dissolving formulation of risperidone, available in 0.5, 1 and 2 mg strengths. Potential candidates may include psychiatric patients on directly observed therapy, or patients with swallowing difficulties. The cost of the orally disintegrating tablets is somewhat higher than the regular tablets, based on either FSS or BPA pricing. Risperidone is not available generically.	Added to the TMOP (line extension)	**Quantity Limits** N/A **Prior Authorization** None	The BCF listing for risperidone was clarified to exclude the orally disintegrating tablets.
Montelukast oral granules (Singulair; Merck)	May 03: New 4 mg oral granule formulation of montelukast. The new formulation is FDA-approved for treating asthma down to 12 months of age, and for treating seasonal allergic rhinitis down to 2 years of age. Previously, the youngest age for which montelukast was indicated was 2 years (4 mg chewable tablets). The oral granules should be mixed with carrots, applesauce, ice cream or rice; they are not to be mixed with liquids. Montelukast is not available generically. The Committee agreed that the new formulation provides an FDA-approved alternative in this age group and is likely to increase the ease of treatment.	Added to the TMOP (line extension)	**Quantity Limits** N/A **Prior Authorization** None	The BCF listing for montelukast oral was clarified to include the oral granules.

APPENDIX B: FORMULARY STATUS OF NEWLY APPROVED DRUGS NOT REQUIRING FORMAL REVIEW BY THE P&T COMMITTEE

Generic name (Trade name; manufacturer)	**Comments**
Omeprazole magnesium delayed release tablets, OTC (Prilosec OTC; Proctor and Gamble))	Indicated for treatment of frequent heartburn symptoms. Therapy should not be continued beyond 14 days. Available as 20.6 mg tablets in the magnesium salt form, which is equivalent to 20 mg of omeprazole. The over-the counter (OTC) product is not AB rated to Rx omeprazole. Prilosec OTC is anticipated to cost $0.80/tablet, but it will be packaged in blister cards of 14, 28, or 42 tablets, which may limit its usefulness to local MTFs considering formulary addition. Prescription omeprazole will remain on the market. Prices for the prescription products: Rx Prilosec: $2.11/cap (FSS); Rx generic omeprazole: $2.89/cap (retail). Prilosec OTC was not considered for addition to the BCF, since it is an OTC product. Currently there are two proton pump inhibitors (PPIs) on the BCF in an open class: rabeprazole and lansoprazole. Prilosec OTC was not added to the TMOP Formulary, since OTC agents are not a covered TRICARE benefit.
Desloratadine orally disintegrating tablets (Clarinex Redi Tabs; Schering)	Automatically added to the TMOP Formulary as a line extension. Not considered for the BCF because desloratadine (Clarinex) is not a BCF item.
Agalsidase beta (Fabrazyme; Genzyme)	Orphan drug for treating Fabry disease. Administered by IV infusion every 2 weeks. Not considered for the TMOP Formulary because it is not intended for self-administration. Not considered for the BCF due to the specialized nature of the medication.
Laronidase (Aldurazyme; Genzyme))	Orphan drug for treating the Hurler and Hurler-Scheile forms of mucopolysaccharidoses I. Administered by IV infusion q week. Not considered for the TMOP Formulary because it is not intended for self-administration. Not considered for the BCF due to the specialized nature of the medication.
Bortezomib (Velcade; Millennium Pharmaceuticals)	Proteasome inhibitor (new class of anti-cancer drugs). Third-line treatment for multiple myeloma. Administered by IV bolus injection twice/week for two weeks, followed by 10 days off therapy. Not considered for the TMOP Formulary because it is not intended for self-administration. Not considered for the BCF due to the specialized nature of the medication.
Tositumomab & I 131 tositumomab (Bexxar; Corixa Corp)	Monoclonal antibody in combination with radiation for non-Hodgkin's lymphoma. Administered by nuclear medicine. Not considered for the TMOP Formulary because it is not intended for self-administration. Not considered for the BCF due to the specialized nature of the medication.
Carbidopa / levodopa / entacapone (Stalevo; Novartis / Orion)	Combination of Anti-Parkinson's agents carbidopa/levodopa with entacapone (Comtan), a catechol-O-methyltransferase [COMT] inhibitor. Entacapone is always given with carbidopa/levodopa, and never administered by itself. The combination product is indicated for treating Parkinson's Disease patients who experience end-of-dose wearing off. Automatically added to the TMOP Formulary as a new combination of drugs already available. Not considered for the BCF since entacapone is not listed on the BCF.
Ondansetron orally disintegrating tablets (Zofran ODT; GSK)	Automatically added to the TMOP Formulary as a line extension. Not considered for the BCF because ondansetron is not listed on the BCF.
Olmesartan medoxomil /HCTZ tablets (Benicar HCT; Forest/Sankyo)	ARB in combination with HCTZ. Automatically added to the TMOP Formulary as a line extension. Not considered for BCF addition as ARB contracting initiative is in progress.
Atazanavir (Reyataz; BMS)	Protease inhibitor approved for use in combination with other antiretroviral agents for HIV. First once daily protease inhibitor. Automatically added to TMOP as an HIV agent. Not considered for the BCF due to the specialized nature of the medication.
Emtricitabine (Emtriva; Gilead)	NNRTI (non-nucleotide reverse transcriptase inhibitor) for HIV. Automatically added to TMOP as an HIV agent. Not considered for the BCF due to the specialized nature of the medication.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING, THE DOD P&T COMMITTEE MEETING, AND THE JULY 2003 INTERIM "E-MAIL" MEETING OF THE DOD P&T EXECUTIVE COUNCIL

1. **BCF CHANGES**

   A. *Additions to the BCF*

      1) Polymycin B Sulfate/Trimethoprim Ophthalmic Solution
      2) Erythromycin Ophthalmic Ointment
      3) Insulin Aspart (Novolog) vials

   Interim Meeting Decisions

      4) Latanoprost (Xalatan)
      5) Rosiglitazone (Avandia)
      6) Rosiglitazone/metformin (Avandamet)
      7) Zolmitriptan oral tablets (Zomig)

   B. Deletions, changes, clarifications or exclusions from the BCF

   Interim Meeting Decisions

      1) Serevent MDI – removed from the BCF due to market withdrawal. The remaining dry powder salmeterol formulation (Serevent Diskus) will be on the BCF.
      2) Sumatriptan oral tablets (Imitrex) – removed from the BCF due to award of the triptan contract.

2. **TMOP FORMULARY CHANGES**

   A. *Additions to the TMOP Formulary*

      1) Moxifloxacin ophthalmic solution 0.5% (Vigamox)
      2) Oxybutynin transdermal system (Oxytrol)
      3) Testosterone buccal system mucoadhesive (Striant) – quantity limits apply, see below

   Interim Meeting Decisions

      4) Gefitinib (Iressa) – quantity limits apply, see below

   B. Exclusions from the TMOP Formulary

      1) Pravastatin/buffered aspirin (Pravigard PAC)
      2) Influenza nasal vaccine (FluMist)

   C. Deletions, changes, or clarifications to the TMOP Formulary

   Interim Meeting Decisions

      1) Lovastatin extended release (Altocor) – Interim Meeting Decision

3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**

   A. Quantity limit for testosterone buccal system mucoadhesive (Striant):

   - TMOP: day supply limit of 90 days (same exception to usual 30-day supply limit for controlled substances as other topical testosterone products); quantity limit of 3 cartons (180 systems) per 90 days
   - Retail: 1 carton (60 systems) per 30 days

   B. Quantity limits for gefitinib (Iressa):

   - TMOP: day supply limit of 45 days; quantity limit of 45 tablets per 45 days
   - Retail: day supply limit of 30 days; quantity limit of 30 tablets per 30 days

4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION PROGRAM**

   A. The PA criteria for etanercept (Enbrel) were changed to reflect the recent FDA indication for ankylosing spondylitis. The revised form is available on the PEC website.

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **5 August 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council convened at 0800 hours on 5 August 2003 at the TRICARE Management Activity (TMA), Falls Church, VA.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
COL Mike Heath, MS (For MAJ Travis Watson, MS)	Army
LtCol Kimberly May, MC (For COL John R. Downs, MC)	Air Force
Col Bill Sykora, MC	Air Force
LtCol Phil Samples, BSC (For LtCol George Jones, BSC)	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Chuck Bruner	Coast Guard
Francine Goodman (For Mike Valentino)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
Col Ardis Meier, BSC	Air Force Pharmacy Consultant
MAJ John Howe, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC (via VTC)	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC (via VTC)	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC (Via VTC)	DoD Pharmacoeconomic Center
Shana Trice (via VTC)	DoD Pharmacoeconomic Center
Dave Bretzke (via VTC)	DoD Pharmacoeconomic Center
Angela Allerman (via VTC)	DoD Pharmacoeconomic Center
Eugene Moore (via VTC)	DoD Pharmacoeconomic Center

3. REVIEW MINUTES OF LAST MEETING

A. The Council approved the minutes of the last meeting with a correction in Table Two Section 7A: the $7.84 average monthly cost for Estraderm was based on an incorrect dosing frequency of once a week. The correct dosing frequency is twice a week, so the correct average monthly cost for Estraderm is $15.68.

B. The Council approved the minutes of the July interim "email" meeting (Appendix A) with an amendment of the thiazolidinedione (TZD) section.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

The July interim "email" DoD Executive Council Meeting resulted in the following BCF and TMOP changes:

- Latanoprost (Xalatan) was added to the BCF
- Rosiglitazone (Avandia) was added to the BCF
- Rosiglitazone/metformin (Avandamet) was added to the BCF
- Serevent MDI was removed from the BCF due to market withdrawal. Serevent DPI will be the remaining salmeterol on the BCF.
- Zolmitriptan oral tablets (Zomig) were added to the BCF
- Sumatriptan oral tablets (Imitrex) were removed from the BCF
- Gefitinib (Iressa) was added to the TMOP with quantity limits
- Lovastatin extended release (Altocor) was removed from the TMOP

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARDS, RENEWALS AND TERMINATIONS

A. The next option years were exercised for the following contracts: fluoxetine, indomethacin, digoxin, naproxen, ointment base, captopril, paclitaxel injection, carbidopa/levodopa SA tablets, glyburide, amantadine, buspirone, benztropine.

B. New contracts were awarded for ketoconazole cream, midazolam, pamidronate injection and zolmitriptan.

6. PROCUREMENT INITIATIVES

A. Oral Fluoroquinolones, Angiotensin Receptor Blockers (ARBs), and Bisphosphonates –CDR Briski updated the Council on the progress of the oral fluoroquinolone, ARB and bisphosphonate solicitations.

B. 2nd Generation Antihistamines – Loratadine is available to MTFs at $0.38 per dose compared to fexofenadine at $0.85 per dose and cetirizine at $0.96 per dose. Although fexofenadine currently remains on the BCF, the termination of the fexofenadine contract allows MTFs to have additional non-sedating antihistamines on their formularies. Since loratadine is significantly less expensive than all other second generation antihistamines, MTFs are encouraged to add loratadine to their formularies and maximize the use of loratadine consistent with the clinical needs of patients. [Note: The Council could not add loratadine to the BCF because over-the-counter products are generally not allowed on the BCF.] Loratadine is currently on 52% of MTF formularies.

C. Novo Insulin Products – CAPT Torkildson presented information on two issues regarding the current contract with Novo Nordisk for regular, NPH, lente, and 70/30 insulin products.

1. The Council voted at its last meeting to recommend that DSCP not exercise the final option year on the insulin contract (which covers regular, NPH, 70/30 and lente insulin), and solicit a new contract this year. This recommendation was based on the increasing utilization of both ultra-short acting insulin and alternative insulin delivery systems, neither of which is covered by the current contract. Novo approached the PEC in mid-June with a proposal to lower the FSS price on their FlexPen disposable delivery systems and continue their temporary price reduction for Novolog vials (32% reduction from the FSS price) and Novolog 70/30 vials (53% reduction from FSS) in return for a decision to exercise the final option year of the contract. Since the last meeting the PEC also received information that a third company anticipates approval of their ultra-short acting insulin product early next year.

2. Shortly after its meeting with the PEC in mid-June, Novo notified the PEC that they planned to discontinue distribution of their lente insulin product in October 2003. Novo committed to providing lente insulin to their government clients at current levels through January 2004. An analysis of PDTS data revealed that only 271 patients filled prescriptions for lente insulin at MTFs and only 63 patients filled prescriptions for lente insulin in mail order during the 2nd quarter of FY2003. The number of patient utilizing lente insulin decreased by 50% over

the previous year. Although lente insulin is covered by the current insulin contract, the discontinuation of lente insulin will affect a relatively small number of patients.

The PEC recommended that the council reverse its previous decision and instead recommend that DSCP exercise the final year of the insulin contract and delay a resolicitation of the contract until summer 2004. The Council voted unanimously to exercise the final option year of the insulin contract and defer the resolicitation of insulin contract until next summer.

7. DRUG/DRUG CLASS EVALUATIONS

A. Oral Estropipate Hormone Replacement Therapy – Hormone replacement therapies currently available on the BCF include oral conjugated estrogens (Premarin), oral medroxyprogesterone, combination conjugated estrogen/medroxyprogesterone (Prempro), estrogenic vaginal cream (MTFs select the brand), and estradiol transdermal systems (Esclim). The Council considered oral estropipate for addition to the BCF as an alternative oral estrogen replacement therapy.

Efficacy/Safety/Tolerability – Studies have shown that the various oral estrogen replacement products are equally efficacious in treating postmenopausal symptoms. The labeling for all oral estrogen products contains the same safety warning for the risk of heart disease, stroke, and cancer. There is no evidence that the oral estrogen products differ in tolerability.

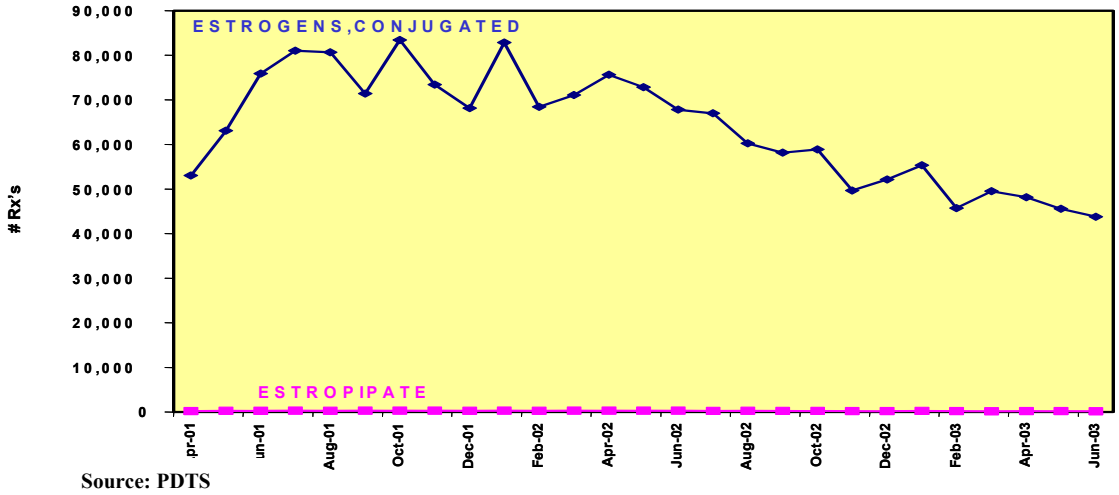
Table 1: Prime Vendor Weighted Average Cost/Tablet for Estropipate and Premarin

	Estropipate (Mylan)	**Estropipate (**Watson)	**Estropipate** (Ogen; Pharmacia & UpJohn	**Estropipate** (Ortho-est; WHFC)	**Conjugated Estrogen** (Premarin; Wyeth-Ayerst)
Prime Vendor Weighted Average Acquisition Cost/Tablet (June 2003)	$0.41	$0.11	$0.18	$0.19 (Was $0.42 prior to BPA initiated in June)	$0.23

Cost – Table 1 displays the prime vendor weighted average cost/tablet for various brands of estropipate and Premarin. Estropipate is available at a significantly lower cost than Premarin.

Other factors – The FDA and American College of Obstetricians and Gynecologists (ACOG) recommend starting women on low doses of estrogen in light of the Women's Health Initiative (WHI) study. Estropipate is not currently available in doses that are equivalent in estrogenic activity to the 0.3 mg and 0.45 mg strengths of Premarin.

Figure 1: MTF Oral Estrogen Rx Fills April 01 – June 03



Source: PDTS

Utilization – Figure 1 shows that MTFs use very little estropipate in comparison to Premarin. Only 20% of MTF formularies include estropipate compared to the 98% that include Premarin. Providers who were surveyed stated that the addition of estropipate to the BCF would not likely cause them to substantially increase their use of estropipate in lieu of Premarin.

The Council voted unanimously to not add an estropipate to the BCF because there is no evidence at this time that prescribers would be willing to use estropipate in lieu of Premarin.

B. *Dopamine Agonists* - The PEC is working with the VA on a joint review of the dopamine agonists. After the review is completed, the PEC will estimate the relative cost-effectiveness of the dopamine agonists and recommend which, if any, dopamine agonists, to add to the BCF.

C. *Isotretinoin*

Isotretinoin, a synthetic analogue of Vitamin-A, is indicated for the treatment of recalcitrant nodular acne. Available from Roche pharmaceuticals as Accutane® since 1982, isotretinoin recently became available as an AB-rated generic from three other manufacturers. The oral isotretinoin products available in the United States as of 1 July 2003 are listed in Table 2.

The Council considered an abbreviated PEC drug class review of isotretinoin for the purpose of deciding whether to pursue a sole-source contract (i.e. a contract to exclusively use a single brand of isotretinoin). Although sole-source contracts for "A-rated" generic equivalents do not typically require the review of the Council, an exception was made for isotretinoin because of its association with severe adverse events.

Table 2: Isotretinoin Products Available in the United States as of July 2003

Brand Name	Dosage Strengths	FDA approval date	Manufacturer
Accutane	10, 20, 40 mg	May 7, 1982	Hoffman – La Roche
Amnesteem	10, 20, 40 mg	Nov 15, 2002	Bertek
Sotret	10, 20, 40 mg	Dec 24, 2002	Ranbaxy labs
Claravis	10, 20, 40 mg	Apr 11, 2003	Barr

An average of 2,500 isotretinoin prescriptions are dispensed each month to DoD beneficiaries. Of these, approximately 1,500 are filled at MTFs and 1,000 through the retail network at costs of $342,000 and $221,000 respectively. The mail order system does not fill isotretinoin prescriptions because of the difficulty in meeting the requirements of the FDA mandated safety programs. The cost of a typical course of therapy for one person (15 weeks) is approximately $1,000 if the medication is dispensed through an MTF and $1,265 if the medication is dispensed through the retail network.

Efficacy/Safety – Isotretinoin has been on the market for over 20 years and remains the most efficacious treatment available for recalcitrant nodular acne. The main issue related to isotretinoin therapy is its potential to cause serious adverse effects, the most serious of which are birth defects and psychiatric disorders. In response to these adverse events, the FDA now requires that all isotretinoin therapy be administered in accordance with its strict risk management criteria.

Contracting Issues – The factors providing the impetus to pursue a sole-source contract for isotretinoin are its high cost, availability from multiple sources, and continued wide use within the MHS. The main issues to be addressed in pursuing a sole-source contract for isotretinoin include: (1) the interchangeability of the products, (2) the interchangeability of the risk management programs, and (3) the interchangeability of the prescription sticker programs.

1. Interchangeability of isotretinoin products: All four isotretinoin products available in the United States are AB-rated. By definition this means they are interchangeable.
2. Interchangeability of risk management programs: The FDA requires that the risk management programs for all isotretinoin manufacturers be the same. This is evident based on a statement by Janet Woodcock, Director of the Center for Drug Evaluation and Research, FDA that was found on the FDA web page: "All generic brands of isotretinoin will utilize the labeling that is alike in all material respects to the name brand, educational tools, and follow-up metrics in place under S.M.A.R.T." S.M.A.R.T. is the risk management program of the innovator company – Roche. To confirm this, written information included in three of the four risk management programs (SMART, SPIRIT, IMPART) were compared by members of the PEC and found to be identical in their wording. The risk management programs for each of the available products are listed in Table 3.
3. Interchangeability of prescription stickers: In a phone discussion with a Roche pharmaceutical representative regarding the interchangeability of isotretinoin

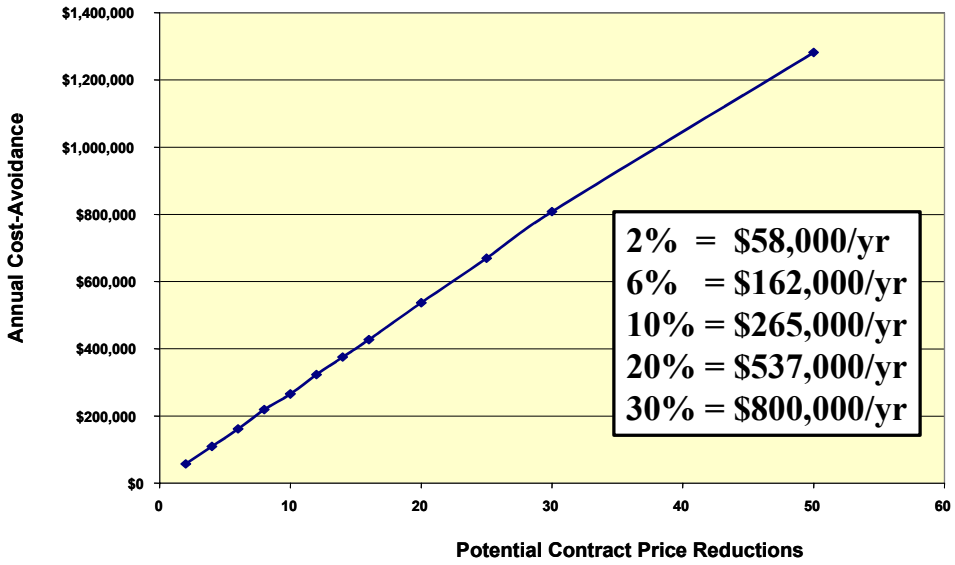
sticker programs, the following oral statement was provided: "Any AB-rated isotretinoin can be substituted for a prescription with an Accutane sticker and Accutane can be substituted for any prescription with an AB-rated isotretinoin sticker." Representatives from a state board of pharmacy (Texas) and the FDA concurred with this statement.

Table 3: Isotretinoin Risk Management Programs

Brand Name	Manufacturer	Safety Program
Accutane	Hoffman-La Roche	S.M.A.R.T. (System to manage Accutane related teratogenicity)
Amnesteem	Bertek	S.P.I.R.I.T. (System to prevent isotretinoin related issues of teratogenicity)
Sotret	Ranbaxy labs	I.M.P.A.R.T. (Isotretinoin medication program alerting you to the risks of teratogenicity)
Claravis	Barr	A.L.E.R.T. (Adverse event learning and education regarding teratogenicity)

Potential Cost-Avoidance – Figure 2 illustrates the cost-avoidance that would result from various price reductions that might be obtained with a sole-source contract for isotretinoin.

Figure 2: Isotretinoin cost avoidance from potential contract price reductions



The Council voted unanimously to support a sole-source contract initiative for isotretinoin that does not mandate addition of isotretinoin to the BCF.

8. REQUESTS FOR BCF CHANGES

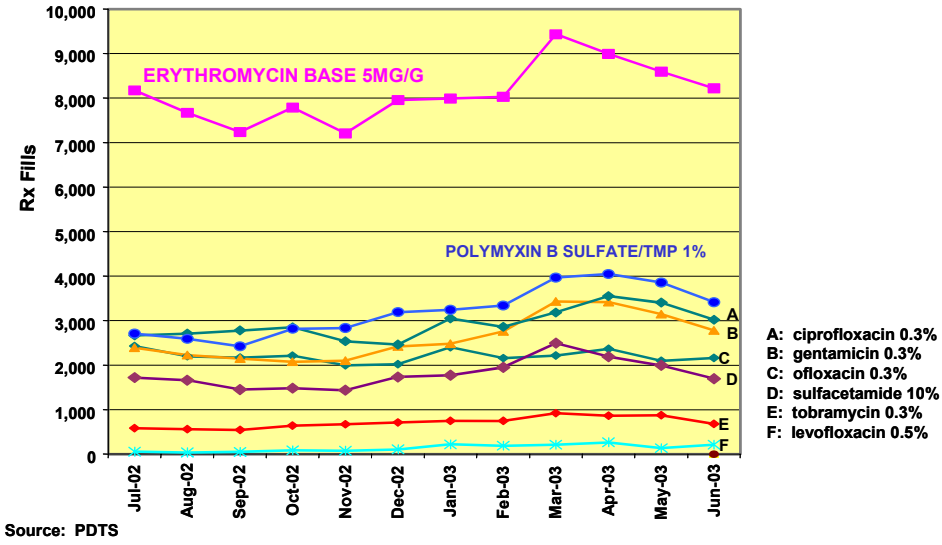
A. Ophthalmic Antibiotics – Polymyxin B Sulfate/Trimethoprim and Erythromycin

CDR Graham presented a recommendation from the PEC that polymyxin B sulfate/trimethoprim and erythromycin ophthalmic antibiotics be added to the BCF. This recommendation was based on two factors: 1) both are cost-effective alternatives compared to ophthalmic fluoroquinolones for primary care treatment of superficial ocular bacterial infections, including acute bacterial conjunctivitis and blepharoconjunctivitis, and 2) high utilization and formulary status in the MTFs.

Efficacy/Safety/Tolerability – Polymyxin B sulfate/trimethoprim and erythromycin have been proven efficacious in the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by susceptible organisms. Erythromycin is also safe and effective for the prophylactic treatment of ophthalmia neonatorum due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Safety and effectiveness of polymyxin B sulfate/trimethoprim are established down to the age of 2 months.

Cost – Both polymyxin B sulfate/trimethoprim and erythromycin are available as generics with respective costs of $1.19 – 1.52/10 ml vial and $0.99/3.5 gm tube, compared to fluoroquinolones starting around $14.00/5 ml.

Figure 3: MTF Rx Fills Ophthalmic Antibiotics July 02 – June 03



Source: PDTS

Utilization/MTF Formulary Status – Figure 3 shows current MTF utilization of polymyxin B sulfate/trimethoprim and erythromycin compared to other ophthalmic antibiotics. Over 80% of MTFs have both agents on their formulary.

The Council voted unanimously to add polymyxin B sulfate/trimethoprim ophthalmic solution and erythromycin ophthalmic ointment to the BCF.

B. Ultra-Short Acting Insulin Products

CAPT Torkildson and Ms. Angela Allerman presented a recommendation from the PEC that an ultra-short acting insulin product be added to the BCF. This recommendation was based on two factors: 1) the superior outcomes achieved with ultra-short acting insulin compared to regular insulin, and 2) the steadily increasing utilization of ultra-short acting insulin products in DoD.

Data were presented comparing the activity profiles of regular and ultra-short acting insulins. The more rapid onset of action, shorter time to peak activity, and shorter effective duration of action make the profile of ultra-short acting insulin more physiologic. Clinical trials demonstrate improved post-prandial glycemic control, lower HbA1c levels, and fewer episodes of post-prandial hypoglycemia with ultra-short acting insulins.

Data regarding the relative utilization of regular and ultra-short acting insulin at MTFs is presented in Table 4. The projected figures are based on the trend observed over the preceding 12 months. Based on these projections, the number of utilizers of ultra-short acting insulin products will exceed the number of regular insulin utilizers during the first quarter of FY 2004. Based on this information, the Council voted unanimously to accept the PEC's recommendation to add an ultra-short acting insulin to the BCF.

Table 4: Number of Unique Utilizers of Ultra-short Acting and Regular Insulin Products at MTFs

Quarter	Ultra-short Acting	Regular
Historical Figures		
2001, Q4	4,219	13,507
2002, Q1	4,784	13,210
2002, Q2	5,378	12,733
2002, Q3	6,055	12,289
2002, Q4	6,569	11,455
2003, Q1	7,456	11,316
2003, Q2	8,032	10,703
Projected Figures		
2003, Q3	8,638	10,248
2003, Q4	9,280	9,767
2004, Q1	9,922	9,285
2004, Q2	10,564	8,804
2004, Q3	11,206	8,322
2004, Q4	11,848	7,841

The presentation now turned to the question regarding which ultra-short acting insulin represented the most cost-effective choice for the direct care system. Data were first presented that addressed the therapeutic interchangeability, clinical coverage, and provider acceptance of Novolog and Humalog. The available data suggest no clinically relevant difference between the products' activity profiles. Although Novolog has an FDA-approved indication for use in insulin pumps and Humalog does not, several trials including a non-blinded head-to-head trial in pump patients suggest that the products are equally effective in improving post-prandial glucose control in this population. Anecdotal reports exist that suggest Novolog has greater stability and maintenance of potency in pumps, especially in warm climates, but this has not been scientifically evaluated as yet. There is no evidence for a difference in the number, type, or severity of adverse reactions seen with the two products. Therefore, either product appears to be suitable for use in diabetic patients. Either product could reasonably be expected to meet the clinical needs of the majority of patients requiring pre-prandial insulin therapy to control post-prandial hyperglycemia. Conversely, patients who failed to achieve the desired control with one of these products would be unlikely to achieve the desired control with the other.

Assessment of provider acceptance in this case was somewhat complex. As noted previously, Novo Nordisk currently has a contract to provide regular, NPH, and 70/30 mixed insulin to the DoD and VA. DoD compliance with this contract is fairly good, with about 75% of utilizers in each of these market baskets using the Novo product. However, < 3% of utilizers of ultra-short acting insulin use Novolog, despite an $8/vial cost difference in favor of Novolog. Additionally, at the time of the analysis Novolog was on formulary at only 4 MTFs throughout DoD. In a recent *PEC Update*, readers were asked to comment on why this situation existed. Responses indicated that several factors contributed to this: 1) Humalog was first to market and first on formulary (inertia); 2) providers considered the products to be clinically equivalent and were unaware of the price difference; and 3) Novolog was not on formulary at most facilities, and as the products were not seen as having substantial clinical differences providers had no motivation to push for its addition. Both junior and senior level endocrinologists expressed a willingness to change to the less expensive product, and one diabetic educator stated that she had unsuccessfully approached her local P&T Committee on three different occasions with evidence that substantial cost savings could be realized by making Novolog available to providers.

The following cost and utilization data were then presented. During the period 1 May 2002 through 30 April 2003, $3.2 million were spent on ultra-short acting insulin therapy by MTFs. Given the growing utilization of ultra-short acting insulin, it was projected that in FY 2004 MTFs would experience an 18.6% increase in the cost of ultra-short acting insulin therapy, to $3.8 million. However, given the current prices of the two products, if only 10% of the market was moved to Novolog the MTFs would experience instead a 2% decrease in the cost of therapy. If Novolog achieved a 50% market share, the overall cost would decrease by almost 15%, to $2.7 million, despite an almost 20% increase in utilization. The increase in

market share would also ensure that the Novolog prices would remain in place until the awarding of the new insulin contract next fall.

Based on these factors, the Council voted unanimously in favor of the PEC recommendation to add Novolog to the BCF, to have the PEC provide information to providers and facilities encouraging its use for the reasons noted, and to have the PEC provide additional information regarding the opportunity for facilities to achieve additional cost avoidance by evaluating the Novo FlexPen devices as an alternative to Humalog disposable syringes.

9. ADJOURNMENT

The meeting adjourned at 1400 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Thursday, 13 November 2003. All agenda items should be submitted to the co-chairs no later than 06 October 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

APPENDIX A: MINUTES OF THE DEPARTMENT OF DEFENSE (DOD) PHARMACY AND THERAPEUTICS (P&T) "EMAIL" INTERIM EXECUTIVE COUCIL MEETING

NOTE: Amended version (section 4B) approved by the DoD P&T Executive Council at their regularly scheduled meeting, 5 August 2003.

Department of Defense Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **14 July 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) "Email" Interim Executive Council Meeting

1. The DoD P&T Executive Council held an interim meeting by email on 9 July 2003 in order to make some decisions that the co-chairs felt should not be delayed until the August meeting. All voting members posted email responses by close of business 14 July 2003.

2. VOTING MEMBERS RESPONDING

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard

VOTING MEMBERS ABSTAINING

Mike Valentino	Department of Veterans Affairs

3. NATIONAL PHARMACEUTICAL CONTRACT AWARD

The VA National Acquisition Center (NAC) recently awarded a joint VA/DoD triptan contract to Astra Zeneca for zolmitriptan. Per the terms of the contract, zolmitriptan replaces sumatriptan as the only oral triptan on the BCF effective 11 Jul 03. MTFs may have one oral triptan in addition to zolmitriptan on their local formularies. The contract does not affect the formulary status of non-oral triptan dosage forms. The PEC provided guidance to MTFs for implementing the zolmitriptan contract (see the National Contracts page on the PEC website). Sumatriptan injection will remain on the BCF.

4. PROCUREMENT INITIATIVES

A. Ophthalmic Prostaglandins – At the May DoD P&T Executive Council meeting the Council was informed that the VA and DoD would each pursue their own procurement strategies for ophthalmic prostaglandins. Pfizer has proposed a blanket purchase agreement (BPA) that reduces the price of latanoprost by 25% (price decreases from $28.89 to $21.67 per bottle) if latanoprost is added to the BCF and no other ophthalmic prostaglandins are included on the BCF. Latanoprost would be the sole ophthalmic prostaglandin on the BCF, but MTFs could have additional ophthalmic prostaglandins on their local MTF formularies. The Council voted unanimously to add latanoprost to the BCF and advise DSCP to approve the latanoprost BPA.

B. Thiazolidinediones (TZDs, "Glitazones") – The Council had previously authorized the addition of a single thiazolidinedione to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contracting strategy competing rosiglitazone and pioglitazone. Glaxo Smith Kline (GSK) has proposed a joint VA/DoD BPA that offers tiered pricing for rosiglitazone (Avandia) and the combination of rosiglitazone and metformin (Avandamet) based on their aggregate market share at MTFs if Avandia and Avandamet are the only thiazolidinediones on the BCF. The Avandamet BPA price equals the rosiglitazone BPA price plus the contract price for generic metformin. The BPA pricing will provide a 20% discount to DoD based on the 68% market share that rosiglitazone currently has at MTFs. Based on historical dose distributions, the 20% discount will reduce the average daily cost for rosiglitazone from $2.16 to $1.73. The average daily cost for pioglitazone is $2.41, which is 39% more per day than rosiglitazone.

Although the Council had not previously discussed the inclusion of Avandamet in the TZD procurement strategy, the Council determined that the addition of Avandamet was consistent with previous BCF decisions and would be a rational complement to Avandia on the BCF because:

- Metformin is appropriately and frequently used in combination with rosiglitazone (50% of current rosiglitazone users are also taking metformin).
- The Council has previously concluded that combination products may be more convenient for patients to take and may improve compliance compared to giving the same products separately.
- The Avandamet pricing is cost-neutral compared to the pricing for the separate products. Although DoD currently has a contract for metformin, there have been

supply problems that cause MTFs to make off-contract purchases of metformin at higher prices. To the extent that the use of Avandamet will reduce the use of off-contract metformin, DoD will realize a cost-benefit for those patients needing combination therapy.

The Council voted unanimously to add rosiglitazone (Avandia) and the combination of rosiglitazone and metformin (Avandamet) to the BCF and advise DSCP to approve the rosiglitazone BPA.

5. BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES

A. Gefitinib (Iressa) 250 mg tablets – Iressa is a new oral agent approved, 5 May 03, as monotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel (Taxotere) chemotherapies (i.e. third-line treatment).

The Council unanimously voted to not add Iressa to the BCF, but to add Iressa to the TMOP Formulary with a quantity limit of 45 tablets per 45 days, to reduce wastage. Gefitinib is costly ($1168/month based on FSS pricing) and patients are likely to discontinue therapy (2/3 of the patients receiving therapy will be treated for no longer than 3 months), either due to death or lack of response. In addition, since the symptomatic benefit of gefitinib appears to correlate with tumor response rate and occurs early in treatment, it is rational to evaluate the patient within 6 weeks (clinical investigators maintain that four to six weeks of therapy is sufficient to test for response). It also appears reasonable to discontinue therapy in patients who are not benefiting.

B Statins – At the May 03 DoD P&T Executive Council meeting the Council voted to add Altocor to the TMOP Formulary. The PEC has subsequently been advised that the addition of Altocor to the TMOP formulary may violate the provisions of the Zocor contract.

The solicitation for the new stated in part, "The BCF and Mail Order Pharmacy Formulary will also contain a generic form of lovastatin and may contain one of the HMG-CoA agents not extensively metabolized by the cytochrome P450 (CYP) metabolic pathway (i.e. pravastatin or fluvastatin), but not both."

Although the solicitation did not specifically prohibit the inclusion of a brand name version of lovastatin on the TMOP formulary, the specific reference to inclusion of a generic form of lovastatin on the TMOP formulary could reasonably be construed to imply that a brand name version of lovastatin would not be included on the TMOP formulary.

The Council voted unanimously to remove Altocor from the TMOP formulary.

6. NEXT MEETING

The next meeting will be held at TRICARE Management Activity (TMA), conference room 815, Skyline Building 6, 5111 Leesburg Pike, Falls Church, VA at 0800 on Tuesday, 5 August 2003. All agenda items should be submitted to the co-chairs no later than 18 July 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

NOTE: Amended version (section 4B) approved by the DoD P&T Executive Council at their regularly scheduled meeting, 5 August 2003.

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **14 July 2003**

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<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **7 MAY 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 7 May 2003, at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol Ed Zastawny, BSC (For LtCol George Jones, BSC)	Air Force
CDR (sel) Debra Arsenault, MC (For CAPT Matt Nutaitis, MC)	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Dr. Trevor Rabie	Uniformed Services Family Health Plan
Mark Geraci (For Mike Valentino)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
COL Geoffrey Rake, MC (via TC)	Medical Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
COL Mike Heath, MS (via VTC)	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
CAPT Betsy Nolan, MSC (VTC)	Navy Pharmacy Specialty Leader
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
LTC Don DeGroff, MS	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
LtCol Dave Bennett, USAF, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, USAF, MC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board
Lisa LeGette	Express Scripts
Howard Mazzafro	Express Scripts
MAJ John Howe, MS	Defense Supply Center Philadelphia
Gene Lakey	TriWest

3. **REVIEW MINUTES OF LAST MEETING/ADMINISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **INTERIM DECISIONS** – No interim decisions.

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL William Davies, DoD Pharmacy Program Director, TMA, stated that the current plan is to implement the Uniform Formulary in conjunction with the TRICARE Retail Pharmacy contract. The proposed date for implementation of the Tricare Retail Pharmacy (TRRx) is April 2004.

6. **BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES** – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 6 new drugs or formulations (see Appendix A). The PEC also presented brief information on four additional new drugs or formulations not requiring a complete review by the Committee (see Appendix B). The Committee agreed that no further review was required.

7. MAIL ORDER AND RETAIL NETWORK ISSUES

A. *Statins* – The high potency statin contact was awarded to Merck for simvastatin (Zocor). The contract states that the BCF and Mail Order Pharmacy formulary will also contain a generic form of lovastatin and may contain one of the statins that is not extensively metabolized by the cytochrome P450 3A4 isoenzyme system. The Committee voted unanimously to add generic lovastatin, lovastatin extended release (Altocor), lovastatin/Niaspan (Advicor), and pravastatin (Pravachol) to the TMOP formulary.

B. *Guaifenesin* – At the November 2002 meeting, the P&T Committee was informed that:

> "As of 12 Jul 2002, Mucinex (Adams Labs) became the first single ingredient guaifenesin extended release product to be 1) approved as safe and effective under a New Drug Application (NDA) and 2) to be approved as an over-the-counter (OTC) product. As a consequence of approval, the FDA has sent warning letters to manufacturers of guaifenesin extended release products explaining that currently marketed single ingredient guaifenesin extended release products without an approved application are considered misbranded and in violation of section 505(a) of the Food, Drug, and Cosmetic Act (FDCA). In addition, provisions of the Durham-Humphrey amendment (products cannot be marketed as both Rx and OTC products) effectively mean all single ingredient extended release will be OTC products. At least one affected manufacturer is known to be petitioning this action, but it is not known if any single ingredient guaifenesin extended release product other than Mucinex will continue to be available in the near future. *Since single ingredient guaifenesin extended release products are now OTC products, they will no longer be available from the NMOP and will not be included on the NMOP Formulary. Prescription extended release guaifenesin products will be dispensed by the NMOP as long as current supplies permit.*" (Emphasis added)

The FDA subsequently issued a letter to manufacturers in February 2003 that allowed them to continue manufacturing guaifenesin extended release products until 21May 2003 and continue distribution of such products until 23 October 2003. In the absence of additional actions on this matter, it is expected that legend extended release guaifenesin products will be available until early November 2003.

In light of the FDA's action, the Committee clarified the status of guaifenesin on the TMOP formulary. Single ingredient guaifenesin extended release products will remain on the TMOP formulary and be dispensed from the TMOP as long as they are available as legend drugs.

C. *Legend Vitamins* – Several questions have arisen recently regarding the availability of legend vitamins from the TMOP. According to Chapter 7 of the TRICARE Policy Manual, "Vitamins may be cost-shared only when used as a specific treatment of a medical condition." Operationally, the question is "do all prescriptions for vitamins require an individual determination that they meet the above requirement? Conversely, can prescriptions for certain vitamins be determined to be covered by virtue of their FDA-approved indications and the lack of a potential for off-label use that would not meet the above requirement?" An example of such a product would be a combination of

folic acid, cobalamin (B12) and pyridoxine (B6), indicated as "treatment for hyperhomocysteinemia, homocystinuria, dialysis, end stage renal failure and in conditions associated with cardiovascular disease, cerebrovascular disease, and peripheral vascular disease." The single MCSC pharmacy representative present at the meeting indicated that in his region, phone calls are made on all vitamin prescriptions to verify compliance with the above requirement, except in the case of prenatal vitamins prescribed to women under the age of 45, which are presumed to be medically necessary. This exception is based on a decision made by the DoD P&T Committee in July 1998 to continue to provide prenatal vitamins to females under the age of 45 without a requirement to document pregnancy.

The subsequent discussion focused on how to make the determination that vitamins are being prescribed for a specific medical condition. The TMA General Counsel advised that in general this would be an administrative decision that would be handled as a collaborative effort of Express Scripts, the PEC, and the TMA General Counsel. In most cases the P&T Committee would not be involved in this process, but in some circumstances the Committee might determine that a particular legend vitamin product, by virtue of its FDA-approved indication(s) and a low probability of use that would not be covered by TRICARE, could appropriately be placed on the TMOP formulary. He recommended that in that case a specific statement be included in the minutes stating the specific intended use of the product. The Committee took no further action at this time.

D. "*Line extension" rules for the TMOP* –At the last meeting, the Committee asked for a review of the "line extension" rules for the TMOP, which provide for availability of generic equivalents, new dosage forms, and new formulations of products already on the TMOP formulary without a formal Committee decision. These rules were carried over from the previous National Mail Order Pharmacy (NMOP) program, but there are operational differences between the two programs that affect the manner in which the rules are applied.

For the NMOP program, the mail order contractor (Medco) maintained the file of available items and was responsible for applying line extension rules to determine inclusion or exclusion of new products, along with the NMOP Contracting Officer's Technical Representative (COTR). New molecular entities and other products requiring Committee approval were not added to the file of available items until publication of the minutes of the Committee meeting in which they were approved.

For the TMOP program, the task of maintaining computerized rules defining which items are available through the TMOP now rests with WebMD as a part of the Pharmacy Data Transaction Service (PDTS). Instead of a file of available items, those items not included in the TMOP Formulary are "blocked" using a combination of First Data Bank categories and drug classification codes. Accordingly, it is necessary to review the addition of new products to First Data Bank on an ongoing basis in order to identify new molecular entities and other products that require Committee review. This is now being accomplished by the PEC on a weekly basis, with approval by the TMOP Contracting Officer's Representative (COR).

The Committee approved the line extension rules outlined below. The Committee noted that these are guidelines rather than absolute rules, acknowledging the need for the PEC

and TMOP COR to use their judgment to deal with circumstances not covered by the rules:

- Medications outlined below are added to the TMOP Formulary without formal action by the DoD P&T Committee unless the PEC or TMOP COR identifies a reason for the P&T Committee to be involved in the decision:
  - Generic equivalent, new dosage form, or new formulation of an agent already on the TMOP Formulary
  - New drug entity in a therapeutic class/category for which the Committee has previously approved automatic inclusion for new drug entities. Currently the only drug class to which this applies is AIDS/HIV drugs. The Committee will review drugs automatically included under this provision at the next scheduled meeting.
  - New combination products of medications that are already on the TMOP Formulary.

8. **CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS** – Buprenorphine and buprenorphine/naloxone (Subutex/Suboxone) were recently approved for the treatment of opioid dependence and are subject to a controlled distribution process. Subutex/Suboxone are NOT a covered benefit under TRICARE rules. Champus Basic Program benefits; Part 199.4 states: "Drug maintenance programs when one addictive drug is substituted on a maintenance basis (such as methadone substituted for heroin) are not covered. This exclusion applies even in areas outside the United States where addictive drugs are dispensed legally by physicians on a maintenance dosage level."

9. **ADJOURNMENT –** The meeting adjourned at 1030 hours. The next meeting will be held at TRICARE Management Activity (TMA), conference room 815 Skyline Building 6, 5111 Leesburg Pike, Falls Church, VA at 0800 on Wednesday, 6 August 2003. All agenda items should be submitted to the co-chairs no later than 18 July 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY AND THE DOD BASIC CORE FORMULARY (BCF)

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Estradiol acetate vaginal ring (Femring; Galen)	24 Mar 03: Indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause as well as symptoms of vulvar and vaginal atrophy. The ring is designed for self-insertion and delivers a steady estrogen dose for 3 months. Two doses: 50 or 100 mcg released daily.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization:** None	Not added to the BCF **Similar BCF agents:** None
Pegvisomant injection (Somavert; Pfizer)	04 Apr 03: Growth hormone receptor antagonist indicated for the treatment of patients with acromegaly who have failed to respond to currently available therapies, such as surgery, radiation therapy, or other medical therapies, or for whom these therapies are not appropriate. Decreases insulin-like growth factor-1 (IGF-1) concentrations As an orphan drug, usage of this product is expected to be infrequent; however, the product is listed in First Data Bank and ESI anticipates no difficulty obtaining it for patients using the TMOP.	Added to the TMOP Formulary & TMOP Covered Injectables List Intended for self-administration; daily subcutaneous injections; must be refrigerated	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** None
Gatifloxacin ophthalmic solution (Zymar; Allergan)	31 Mar 03: 0.3% solution is indicated for treating bacterial conjunctivitis caused by susceptible strains of bacteria	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None
Cyclosporine ophthalmic solution 0.05% (Restasis; Allergan)	29 Jan 03: 0.05% solution is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS)	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Aprepitant capsules (Emend; Merck)	26 Mar 03 (priority review): A substance P / neurokinin 1 (NK1) receptor antagonist indicated for use in combination with other antiemetic agents for preventing acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy (including high-dose cisplatin). First medication specifically labeled for delayed nausea and vomiting. 125 mg dose on day 1 (1 hour prior to chemotherapy), followed by 80 mg QAM on days 2 and 3. Still requires concomitant administration of ondansetron and dexamethasone	Added to the TMOP Formulary	**Quantity Limits** Rationale for the quantity limits includes the potential for inappropriate use and wastage, FDA requirement for the manufacturer to monitor off label uses; and existing quantity limits for 5-HT3 antagonists. Quantity limits are set to provide for the possibility that chemotherapy is on a 3-week cycle, rather than once per month. Most patients will require less. Packaged in convenience packs (one 125 mg; two 80 mg capsules) and in 30-count bottles **Retail:** Convenience packs: 2 packs per 30 days; 125 mg caps: 2 per 30 days; 80 mg caps: 4 per 30 days **TMOP**: Convenience packs: 6 packs per 90 days; 125 mg caps: 6 per 90 days; 80 mg caps: 12 per 90 days **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** None
Enfuvirtide injection (Fuzeon; Roche/ Trimeris)	13 Mar 03 (accelerated approval). New modality for treating HIV (fusion inhibitor) that blocks the interaction of HIV with CD4+ cells. Indicated for use in combination with other antiretroviral agents for treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Product is self-administered SQ BID, and is available in a convenience kit of 60 vials with supplied diluent. Complicated 100-step manufacturing process has resulted in a limited supply for about 12,000-15,000 patients worldwide. Product will be allotted on a first-come, first-serve basis through a sole distributor, Chronimed. Physicians must enroll patients via fax. Details on the Fuzeon Progressive Distribution Program may be found at www.fuzeon.com. Anticipated yearly cost is $20,000.	Not added to the TMOP Formulary & Covered Injectables List. Due to the restricted distribution process, ESI and the PEC will look into the feasibility of supplying enfuvirtide through the TMOP and readdress the issue at the August DoD P&T Committee meeting	**Quantity Limits** Patient needs are established as part of the distribution process; no specific quantity limits are needed. **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None

APPENDIX B: NEWLY APPROVED DRUGS NOT REQUIRING FULL REVIEW BY THE P&T COMMITTEE

Generic name (Trade name; manufacturer)	**Comments**
Isotretinoin capsules (Claravis; Barr)	AB rated generic to Accutane (Roche brand of isotretinoin). Not added to the TMOP Formulary because isotretinoin is excluded from the TMOP Formulary due to controlled distribution requirements. Generics from Bertek (Amnesteem) and Ranbaxy (Sotret) were evaluated in Mar 2003.
Conjugated estrogen/medroxyprogesterone acetate (Prempro 0.45/1.5; Wyeth)	Low-dose formulation of Prempro contains 0.45 mg of estrogen, and 1.5 mg of progestin (instead of 0.625 / 2.5 mg). Automatically added to TMOP as a line extension. Prempro is on the BCF.
Propranolol extended release capsules (InnoPran XL; Reliant)	Indicated for hypertension; the only beta-blocker formulation specifically indicated for QHS dosing. This product was approved under an NDA and is not a generic equivalent to the other propranolol extended release product, Inderal LA (Wyeth). Generic equivalents to Wyeth's Inderal LA have been discontinued. Innopran XL is available in 80 and 120 mg capsules; Inderal LA in 60, 80, 120 and 160 mg capsules. Automatically added to TMOP as a line extension. Not considered for BCF addition, since the other propranolol extended release product was removed from the BCF in Nov 1999 due both to limited supply (both Inderal LA and generics were manufactured by Wyeth) and low usage in DoD.
Metformin extended release tablets 750 mg (Glucophage XR; Bristol-Meyers Squibb)	Automatically added to TMOP as a line extension. Not considered for the BCF since extended release metformin is specifically excluded from the existing BCF listing for immediate release metformin.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. *Additions to the BCF*

      1) Estradiol transdermal system (Esclim)
      2) Risperidone (Risperdal)
      3) Quetiapine (Seroquel)
      4) Pimecrolimus cream (Elidel)
      5) Nitroglycerin patches (Nitrodur) [Schering brand per existing VA/DoD contract]
      6) Isosorbide mononitrate sustained release [Schwarz Pharma brand per existing VA/DoD contract]

   B. *Deletions, changes, clarifications or exclusions from the BCF* - None

2. **TMOP FORMULARY CHANGES**

   A. *Additions to the TMOP Formulary*

      1) Estradiol acetate vaginal ring (Femring; Galen)
      2) Pegvisomant injection (Somavert; Pfizer) – added to the TMOP Covered Injectables List
      3) Gatifloxacin ophthalmic solution (Zymar; Allergan)
      4) Cyclosporine ophthalmic solution (Restasis; Allergan)
      5) Aprepitant capsules (Emend; Merck) – quantity limits apply, see below
      6) Pravastatin
      7) Lovastatin
      8) Lovastatin extended release (Altocor)
      9) Lovastatin/niacin extended release combination (Advicor)

   B. *Exclusions from the TMOP Formulary* - None

   C. *Deletions, changes, or clarifications to the TMOP Formulary* - None

3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**

   A. Quantity limit for aprepitant (Emend; Merck):

      - Convenience packs (convenience packs contain one 125 mg capsule and two 80 mg capsules): 2 packs per 30-day supply (Retail); 6 packs per 90-day supply (TMOP)
      - 80 mg capsules: 4 capsules per 30 days (Retail); 12 capsules per 90 supply (TMOP)
      - 125 mg capsules: 2 capsules per 30 days (Retail); 6 capsules per 90-day supply (TMOP)

4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION PROGRAM** - None

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **6 May 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1500 hours on 6 May 2003 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol Ed Zastawny, BSC (For LtCol George Jones, BSC)	Air Force
CDR (sel) Debra Arsenault, MC (For CAPT Matt Nutaitis, MC)	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Mike Valentino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC (via VTC)	Navy Pharmacy Specialty Leader
COL Mike Heath, MS (via VTC)	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
COL Ardis Meier, BSC (via VTC)	Air Force Pharmacy Consultant
MAJ John Howe, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LTC Don DeGroff, MS	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
MAJ Mike Terry, BSC	TRICARE Southwest
Mark Geraci	Department of Veterans Affairs, PBM
LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board

3. REVIEW MINUTES OF LAST MEETING

The Council approved the minutes of the last meeting with a correction in the last sentence of the fourth paragraph in section 9A:

- Incorrect sentence: MTFs are currently spending nearly $100,000 per month on cholinesterase inhibitors.
- Corrected sentence: MTFs are currently spending nearly $326,000 per month on cholinesterase inhibitors.

4. ADMINISTRATIVE ISSUES

None

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARD, RENEWALS AND TERMINATIONS

A. The next option years were exercised for the following contracts: oral contraceptives, ticlopidine, valproic acid, nicotine patches, insulin syringes, isosorbide mononitrate, and capsaicin cream.

B. Proposals are being evaluated for the awarding of contracts to procure a sole source of isosorbide dinitrate, tramadol, ketoconazole cream, midazolam, and pamidronate injection.

C. DoD accepted an incentive agreement for methylphenidate (Concerta) that will reduce the price below FSS if performance incentives are met by the government.

6. PROCUREMENT INITIATIVES

A. *Ophthalmic Prostaglandins* – The Council had previously authorized the addition of an ophthalmic prostaglandin to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contracting strategy competing latanoprost, bimatoprost and travoprost, which would not require patients to be switched from one agent to another. The Federal Pharmacy Executive Steering Committee's (FPESC) subcommittee for contracting determined that a joint DoD/VA closed class contract would not meet the needs of both agencies. Each agency will pursue its own procurement strategy.

B. *Second Generation Antihistamines* –The availability of loratadine to MTFs at $0.38 per dose compared to fexofenadine at $0.60 per dose under a joint DoD/VA contract precipitated the decision to not renew the next option year of the fexofenadine contract. Although fexofenadine currently remains on the BCF, the termination of the fexofenadine contract allows MTFs to have additional non-sedating antihistamines on their formularies. Since loratadine is significantly less expensive than all other second generation antihistamines, MTFs are encouraged to add loratadine to their formularies and maximize the use of loratadine consistent with the clinical needs of patients. [Note: The Council could not add loratadine to the BCF because over-the-counter (OTC) products are generally not allowed on the BCF.]

C. *Thiazolidinediones (TZDs, "Glitazones")* – The Council had previously authorized the addition of a single thiazolidinedione to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contracting strategy competing rosiglitazone and pioglitazone. The contracting subcommittee of the Federal Pharmacy Executive Steering Committee is evaluating which procurement strategy would be the most cost-effective and meet each agency's requirements.

D. *Oral Fluoroquinolones* – The Council previously voted to support a joint DoD/VA contract for a "workhorse" fluoroquinolone that would compete levofloxacin and gatifloxacin. Two changes have occurred since that time:

   1) Ortho McNeil raised the price of levofloxacin by almost 40% effective 1 May 2003, and then repealed the price increase. Levofloxacin has been the only oral fluoroquinolone on the BCF for the past several years.

   2) Moxifloxacin recently gained FDA approval for treatment of community acquired pneumonia (CAP).

   The Council reviewed the most current clinical data including efficacy and safety/tolerability of levofloxacin, gatifloxacin and moxifloxacin.

   Efficacy – CAP and urinary tract infections (UTIs) are the primary indications for which fluoroquinolones are currently used. Gatifloxacin and moxifloxacin have broader gram-positive coverage and reduced gram-negative coverage than levofloxacin. All three agents are indicated for the treatment of CAP, chronic bronchitis, acute sinusitis and uncomplicated skin and skin structure infections. In addition, levofloxacin and gatifloxacin have an FDA indication for UTIs (however gatifloxacin will normally only cover approximately 80% of UTI infections because it has less gram-negative coverage). Moxifloxacin is not indicated for treatment of UTIs, which is attributed to less gram-negative coverage and extensive metabolism prior to excretion.

Safety/Tolerability – Adverse events of note include:

1) QTc prolongation with the subsequent potential for *torsade de pointes*. *Torsade de pointes* has been reported in 2 of 1,300,000 gatifloxacin patients, and 1 of 1,000,000 levofloxacin patients. Phase II-IV studies of moxifloxacin treatment in over 7,900 patients resulted in no cardiovascular morbidity attributable to QTc prolongation.
2) Dysglycemia has been associated with the use of gatifloxacin in diabetic patients receiving oral hypoglycemic agents or insulin, and elderly patients (>75yrs) with underlying disease states that increase the risk for dysglycemia.

Infectious Disease consultants stated the concerns regarding QTc prolongation and dysglycemia are probably "over-stated." However, providers should exercise caution when using fluoroquinolones in specific patients with underlying risk factors.

The Council concluded that fluoroquinolones are not sufficiently interchangeable to support a closed class contract. Differences in coverage and safety/tolerability concerns prevent the use of a single agent for all patients. All three fluoroquinolones will provide adequate clinical coverage for the majority of CAP and acute sinusitis infections.

The Council unanimously voted to authorize a procurement strategy that could include up to a joint DoD/VA open class contract competing moxifloxacin, gatifloxacin, and levofloxacin as a "workhorse" fluoroquinolone for the treatment of CAP and acute sinusitis.

E. *5HT1 Agonists (Triptans)* – The joint DoD/VA solicitation closed on 20 December 2002. The Government Accounting Agency (GAO) resolved a protest by ruling in favor of the Government. Detailed MTF guidance will be available on the PEC website when the contract award is announced.

F. *Angiotensin Receptor Blockers (ARBs)* – The Council had previously authorized the addition of a single ARB to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contract. The VA has determined that two ARBs should be on the VA National Formulary (VANF). The Council voted unanimously to accept two contracted ARBs for inclusion on the BCF. The change is expected to have minimal economic impact to DoD, while enhancing the ability of MTFs to effectively treat a wider range of patients using formulary ARBs.

G. The Council was updated on the progress of the bisphosphonate and insulin pen procurements.

7. DRUG/DRUG CLASS EVALUATIONS

A. *Transdermal Estrogen Preparations* – Short-term estrogen therapy remains the gold standard for relief of menopausal symptoms. Oral and transdermal routes are the most frequently used, with oral conjugated estrogens as the most popular estrogen formulation in the DoD and United States. Seven estrogen patches, all containing estradiol in varying strengths, are available in the United States (see Table 1). Currently the BCF contains oral conjugated estrogen, medroxyprogesterone, combination conjugated estrogen/medroxyprogesterone (Prempro), and an estrogenic vaginal cream (MTFs' choice). The BCF does not include an estrogen patch.

Table 1: Estradiol Transdermal Systems Available in the U.S.

Product/ Distributor	Release rate (mg/24 hr)	*Surface area (cm^2)	Delivery System/ Frequency of Administration
Vivelle-Dot Novartis	0.025; 0.0375; 0.05; 0.075; 0.1	2.5; 3.75; 5; 7.5; 10	Matrix Twice weekly
Vivelle Novartis;	0.025; 0.0375; 0.05; 0.075; 0.1	7.25; 11; 14.5; 22; 29	Matrix Twice weekly
Esclim Women First Health	0.025; 0.0375; 0.05; 0.075; 0.1	11; 16.5; 22; 33; 44	Matrix Twice weekly
Alora Procter & Gamble	0.05; 0.075; 0.1	18; 27; 36	Matrix Twice weekly
Climara Berlex	0.025; 0.05; 0.075; 0.1	6.5; 12.5; 18.75; 25	Matrix Once a week
♦**Estraderm** Ciba	0.05; 0.1	10; 20	Alcohol reservoir Twice weekly
Estradiol Mylan	0.05; 0.1	15.5; 31	Matrix Once a week
CombiPatch Aventis	0.05 mg estradiol/ 0.14 mg norethindrone acetate; 0.05 mg estradiol/ 0.25 mg norethindrone acetate	16	Twice weekly

*patch size increases with strength;
♦all drug delivery systems are matrix with the exception of Estraderm which uses an alcohol reservoir

Efficacy – All transdermal estrogen systems substantially decrease the number of hot flashes per week. There is no evidence that one estrogen compound is more effective than another. For relief of postmenopausal vasomotor symptoms, any patch can cover the clinical needs of patients; however, those providing the lowest dose with a wide range of dosing options are preferred by providers.

Safety/Tolerability – All estrogen-containing product package inserts carry an identical safety warning for the risk of heart disease, stroke, and cancer. Oral estrogen requires higher doses than transdermal estrogen. A recent trial assessing changes in C-reactive protein (CRP), a marker for inflammation in blood vessels and cardiovascular risk, suggested that transdermal systems might decrease cardiovascular adverse effects of estrogen. Patients using transdermal systems showed no elevation in CRP levels, while oral estrogens increased CRP levels two-fold.

Tolerability issues associated with the systemic effects of estrogen are similar for patches and oral estrogen. Local reactions due to transdermal patches include burning, erythema, irritation, pruritis, and rash. Reactions to the application site occur in about 10% of women who use reservoir (alcohol-based) patches and in 5% of women utilizing the matrix system. The incidence of skin irritation diminishes when the application site is rotated.

Table 2: Prime Vendor Cost for Transdermal Estrogen Systems

	Vivelle-Dot Novartis	**Vivelle** Novartis	**Alora** P&G	**Climara** Berlex	**Estraderm** Ciba	**Estradiol** Mylan
Prime Vendor Weighted Average Acquisition Cost/Patch	$2.20	$1.81	$1.40	$1.92	$1.96	$2.93
Dosage Frequency	Twice a week	Twice a week	Twice a week	Once a week	Twice a week	Once a week
Monthly Cost	$17.60	$14.48	$11.20	$7.68	$7.84	$23.44

Cost – Table 2 displays the prime vendor cost for various transdermal estrogen systems. Women's First Healthcare has offered a blanket purchase agreement that will make their estradiol patch (Esclim) available at a significantly lower monthly cost than other transdermal estrogen products if Esclim is added to the BCF.

Other factors – Esclim has better adhesiveness than Estraderm, which is currently on 75% of MTF formularies. The percentage of transdermal systems that became detached in the Esclim group was 6% compared to 11.3% in the Estraderm group ($p< 0.001$). (Maturitas 1996; 25)

The Council voted unanimously to add Esclim to the BCF. This will result in uniform availability of a transdermal estrogen product at a substantially reduced monthly cost per patient.

B. *Atypical Antipsychotics*

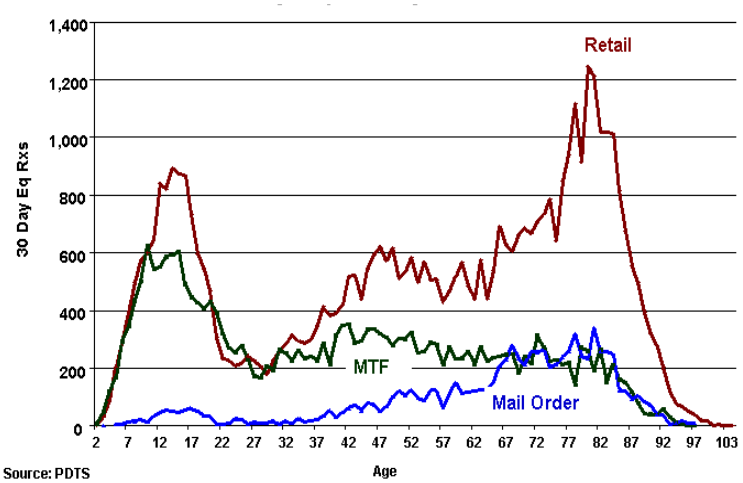
The Council considered a PEC drug class review of five atypical antipsychotics: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). The review did not include clozapine (since its significant risk of agranulocytosis and requirement for routine white blood cell monitoring limit its use) or the injectable formulation of ziprasidone (an immediate release medication not intended for chronic use).

All five agents are indicated for schizophrenia; olanzapine is also indicated for acute bipolar mania. Other uses include depression with psychosis; symptoms of dementia including agitation, hyperactivity, hallucinations, suspiciousness, hostility and uncooperativeness; anxiety disorders; developmental disorders; autism; aggression/self injurious behavior; and Tourette's syndrome. Many of the atypical antipsychotics have been studied in pediatric as well as adult populations, although none of the drugs have pediatric indications. The review categorized the uses for atypical antipsychotics into four groups: schizophrenia and related psychoses, behavioral and psychological symptoms of dementia (BPSD), bipolar mania, and psychiatric and behavioral disorders in children and adolescents.

The onset of both schizophrenia and bipolar disorder is typically in early adulthood, between the late teens and mid-30s for schizophrenia, and in the early 20s for bipolar disorder. Based on the age distribution of usage in DoD (see Figure 1) and the likelihood that individuals with severe psychiatric illnesses will be required to leave the military, it

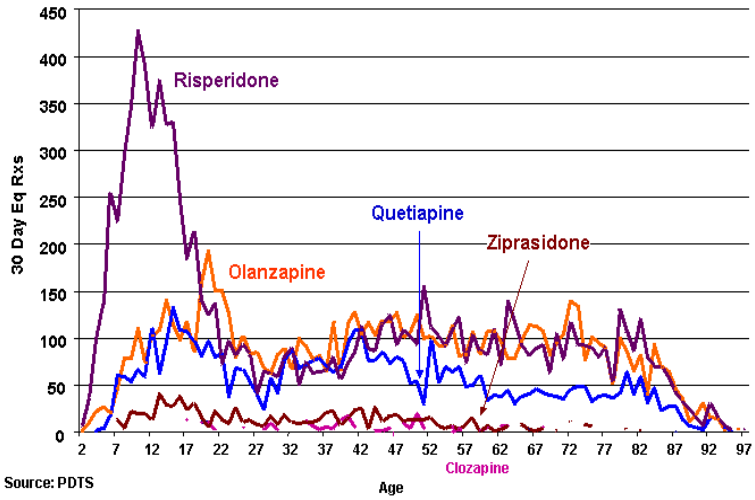
appears probable that uses other than schizophrenia or bipolar disorder represent a substantial proportion of atypical antipsychotic prescriptions in all three points of service.

Figure 1: Age Distribution of Atypical Antipsychotics in DoD
By 30 Day Equivalent Rxs, Oct 02 – Dec 02



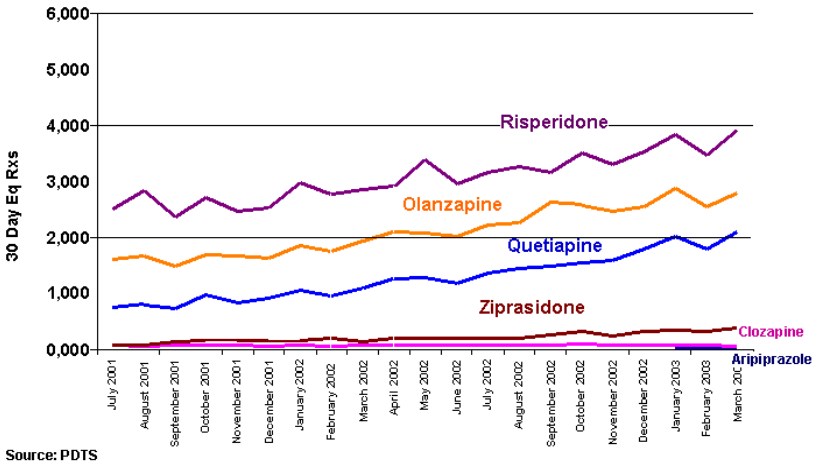
Individual atypical antipsychotics show distinctly different patterns of use at MTFs. As shown in Figure 2 below, risperidone is by far the most commonly prescribed agent in the pediatric population, although there is some usage of other atypical antipsychotics. Olanzapine, quetiapine, and risperidone show similar patterns of use in adult patients, although there is less use of quetiapine overall. Ziprasidone use appears to be less frequent in older patients. Aripiprazole was not yet available during the time period studied.

Figure 2: Age Distribution of Atypical Antipsychotics in MTFs
By 30 Day Equivalent Rxs, Oct 02 – Dec 02



Overall, the most commonly used atypical antipsychotic in MTFs is risperidone, followed by olanzapine and quetiapine (see Figure 3). There is low but increasing use of ziprasidone. Aripiprazole has not been on the market a sufficient period of time to assess its potential use.

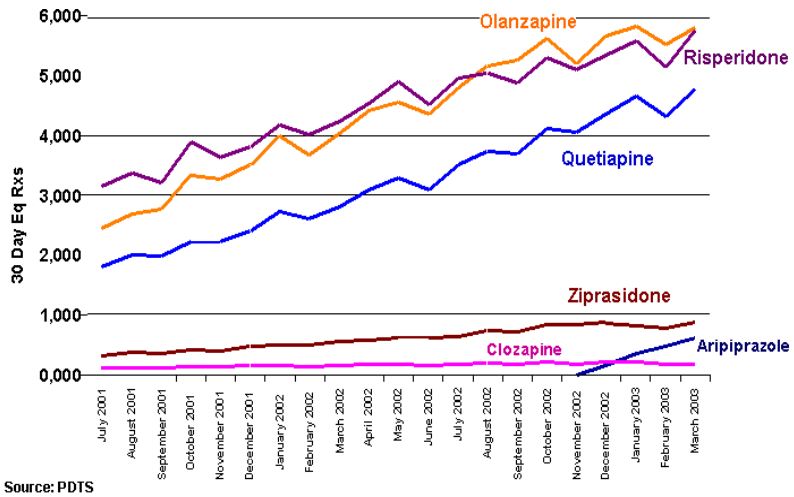
Figure 3: MTF 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Source: PDTS

In the retail network, olanzapine and risperidone are the most commonly used atypical antipsychotics, followed by quetiapine (see Figure 4). Ziprasidone use is again relatively low, but increasing. Aripiprazole use is increasing at a faster rate than in MTFs.

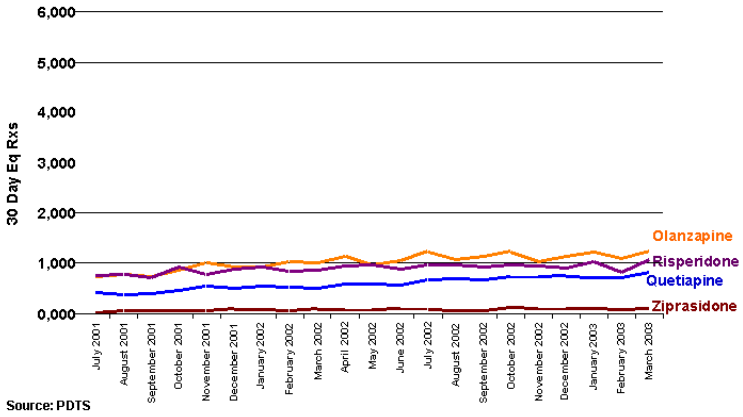
Figure 4: Retail Network 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Source: PDTS

In the mail order program, olanzapine, risperidone, and quetiapine are the most commonly used atypical antipsychotics (Figure 5). Aripiprazole was not added to the mail order formulary until March 03 and does not show on this graph.

Figure 5: Mail Order 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Efficacy

- *Schizophrenia and related psychoses* – There do not appear to be any clinically relevant differences among the atypical agents with respect to overall efficacy and treatment of positive symptoms (e.g., delusions and hallucinations), although individual patients may respond better to one than another. There is stronger evidence with olanzapine than with other atypical antipsychotics to support efficacy in treating negative symptoms (e.g., apathy, lack of motivation, lack of interpersonal and social interaction), based on olanzapine's demonstrated superiority to a typical antipsychotic (haloperidol) in reducing negative symptom scores in both individual short-term and long-term trials. Risperidone has also demonstrated superiority to haloperidol in reducing negative symptom scores based on long-term trials and pooled data from short-term trials. Less clinical evidence is available for quetiapine, ziprasidone, and aripiprazole.

  Atypical antipsychotics have also been shown to have positive effects on neurocognitive functioning (e.g., memory and attention) and mood symptoms (e.g., depressed mood) in patients with schizophrenia or related psychoses; however, the relative efficacy of specific atypical antipsychotics in these domains is still unclear.

- *Dementia* – Dementia is generally defined as a progressive decline in intellectual functioning that impedes normal activities; Alzheimer's dementia is the most common type. The FDA has not yet approved any drugs specifically for the "behavioral and psychological symptoms of dementia" (BPSD). Consensus statements from various national groups recommend antipsychotics as the only available pharmacological treatment for psychotic symptoms of *BPSD*. There is no evidence that any one atypical antipsychotic is more efficacious in one type of dementia than another. Risperidone and olanzapine have been shown to be

efficacious in reducing BPSD in published randomized controlled trials. Other atypical antipsychotics lack published data.

- *Bipolar mania* – According to the American Psychiatric Association Guideline for the Treatment of Patients with Bipolar Disorder (2000), first line treatment for more severe manic or mixed episodes of bipolar disorder is the initiation of lithium or valproate plus an antipsychotic. For less ill patients, monotherapy with lithium, valproate, or an antipsychotic may suffice. The guidelines state that atypical antipsychotics are preferred over typical antipsychotics due to their side effect profile. Olanzapine is the only atypical antipsychotic with an FDA-approved indication for the treatment of bipolar mania. It has been shown to be of comparable efficacy to lithium in the reduction of manic symptoms in one clinical trial and superior to divalproex in another. Olanzapine has also been shown to be superior to placebo as adjunctive therapy with a mood stabilizer (lithium or divalproex). Risperidone has been shown to be superior compared to placebo both as monotherapy and as adjunctive therapy with a mood stabilizer. A recently published trial (April 2003) with ziprasidone showed efficacy for monotherapy. Large trials with aripiprazole and quetiapine (either as monotherapy or as adjunctive therapy) have been performed, but results are not yet available as full publications.
- *Psychiatric and behavioral disorders in children and adolescents* – None of the atypical antipsychotics are currently approved for the treatment of children and adolescents. Multiple small trials, uncontrolled trials, case reports, and case series focus on the use of atypical antipsychotics (most commonly risperidone) in pediatric patients for the treatment of a wide variety of conditions. In large ($n \geq 30$) controlled trials, risperidone has been shown to be efficacious for the treatment of conduct disorder in children with mental retardation (two trials) and for the treatment of aggressive behavior in autistic children (one trial). Quetiapine has been shown to be efficacious as adjunctive therapy for bipolar mania with divalproex in adolescents 12-18 years of age.

Safety/Tolerability

Adverse effect profiles differ substantially among atypical antipsychotics. Provider comments with respect to the safety and/or tolerability of specific agents identified the following concerns: olanzapine (weight gain, diabetes, cholesterol/triglyceride elevations, sedation), quetiapine (weight gain, diabetes, cholesterol/triglyceride elevations), risperidone (EPS, prolactin), ziprasidone (cardiac effects, "emerging case reports of EPS"). Providers commented favorably on the ease of dosing olanzapine compared to quetiapine, and their tendency to use once daily drugs first line. Of the agents, olanzapine and aripiprazole are generally dosed once daily, risperidone can be dosed once or twice daily; and ziprasidone and quetiapine are typically dosed twice daily. Aripiprazole was not yet approved when the survey was completed and was not mentioned by survey responders.

- *Extrapyramidal symptoms* (EPS) are abnormal, involuntary movements associated with antipsychotic treatment. Their occurrence is related to D2 receptor binding in the nigrostriatal pathway; atypical antipsychotics have a higher 5-HT-2 / D2

binding ratio than typical antipsychotics, and thus a lower risk of EPS. This lower risk of EPS is considered to be the defining characteristic of "atypicality." Both olanzapine and risperidone may have increased binding affinity for D2 receptors at higher doses, but in the case of olanzapine, high antimuscarinic activity may limit EPS symptoms.

Of the atypical antipsychotics, risperidone in general appears to have a higher risk of EPS than other agents, although at lower doses (<6 mg/day) this may not be true. Tarsy et al (2002) provide a tentative ranking of EPS risk (from highest to lowest) as follows: Risperidone > olanzapine = ziprasidone > quetiapine > clozapine. Aripiprazole was not included in this review; EPS risk appears low in published trials to date. Accurate determination rates of EPS may be complicated by the presence of carryover EPS effects from previous antipsychotic treatment, particularly in short trials with minimal or no washout periods.

- *Tardive dyskinesia* (TD) is a late-appearing and generally irreversible complication of treatment with long-term antipsychotics, consisting of abnormal postures and involuntary movements of the face, eyes, tongue, trunk, or limbs. Up to 25% of patients may develop TD with cumulative use of typical antipsychotics. Sustained EPS is thought to be a risk factor for the development of TD. In general, atypical antipsychotics appear to have a lower risk of TD than typical antipsychotics. Both olanzapine and risperidone have been shown to be associated with a lower risk of TD than haloperidol. There are no long-term head-to-head studies between atypical antipsychotics addressing the risk of TD and limited long-term data with other atypical antipsychotics.
- *Weight gain* has been reported with a number of atypical antipsychotics, including olanzapine, quetiapine, and risperidone. Allison et al (1999) analyzed clinical trials with atypical antipsychotics and made the following estimates of mean weight gain at 10 weeks (6 weeks for quetiapine, which lacked longer trials; all estimates at midpoint of the standard dosing range): 4.15 kg olanzapine, 2.18 kg quetiapine, 2.10 kg risperidone, 1.08 kg haloperidol, 0.04 kg ziprasidone, -0.74 kg placebo. Aripiprazole was not included in this analysis: the mean weight gain in 4- to 6-week placebo-controlled trials with aripiprazole was 0.71 kg. Later studies and other analyses typically show the same rank order; head-to-head studies comparing olanzapine and risperidone typically demonstrate more weight gain with olanzapine. Weight gain is problematic not only because of adverse health consequences, but because it is frequently associated with lack of adherence to medication.
- *Hyperlipidemia* has been reported with atypical antipsychotics, most commonly with olanzapine, but also with risperidone and quetiapine. Olanzapine and risperidone have been most commonly compared. Increases in total cholesterol appear less frequent with risperidone than with olanzapine; there is little published data from large trials focusing on specific lipid effects (e.g., LDL, HDL, or triglycerides).
- *Treatment-emergent diabetes* has also been reported with atypical antipsychotics. The mechanism is unclear, as is the relationship of treatment-emergent diabetes

with weight gain and hyperlipidemia. In general, schizophrenic patients are at increased risk for hyperglycemia and/or diabetes compared to the general population, whether due to lifestyle factors or as a consequence of the disease process. Diabetes appears to occur more frequently in schizophrenic patients receiving atypical antipsychotics than those receiving typical antipsychotics.

Olanzapine has been associated with the greatest increase in risk of hyperglycemia and diabetes among the atypical antipsychotics reviewed, based on epidemiological studies. Risperidone has also been associated with increased risk, but less consistently and at an apparently lower rate than olanzapine. In one large case-control study (19,637 patients diagnosed and treated for schizophrenia between 1987 and 2000) the incidence of treatment-emergent diabetes per 1000 person-years was 10 for olanzapine (95% CI 5.2 – 19.2), 5.4 for risperidone (95% CI 3.0 – 9.8), and 5.1 for typical antipsychotics (95% CI 4.5-5.8) [Koro et al, 2002]. Data with other atypical antipsychotics is limited.

- *QT interval prolongation* – Labeling for ziprasidone contains a warning about the drug's potential for QTc-interval prolongation and risk of *torsade de pointes* (a potentially fatal arrhythmia) based on the occurrence of prolonged QTc intervals in Phase 2/3 clinical trials. Data from an FDA-requested study assessing the effect of maximum recommended doses of oral ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QTc interval in patients with schizophrenia is available from the FDA Psychopharmacological Drugs Advisory Committee Briefing Document for ziprasidone, July 19, 2000 (available at: www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1.htm). In this open-label, parallel group trial, mean changes in QTc interval occurred in the following rank order, from greatest to least: thioridazine > ziprasidone > quetiapine > risperidone > olanzapine > haloperidol. While ziprasidone was associated with the greatest increase in QTc interval among the atypical antipsychotics studied, no patients had a QTc > 500 msec. The study also included an analysis of the effect of co-administration of metabolic inhibitors for each product. Co-administration of ziprasidone with its metabolic inhibitor, ketoconazole, did not lead to any further prolongation of the QTc despite an increase in serum concentration. According to the manufacturer, there have been no reports of *torsades de pointes* during post-marketing experience with ziprasidone. Ziprasidone has been taken by approximately 150,000 patients since it was approved (Weiden et al, 2002).

  Product labeling for risperidone reports lengthened QTc intervals in some patients but no mean increase even at higher than normal doses. No increases in QTc interval are reported in product labeling for aripiprazole, olanzapine, or quetiapine.

- *Cerebrovascular events* – Results of an analysis of 4 placebo-controlled trials (4-12 weeks in duration) in more than 1200 patients with Alzheimer's disease or vascular dementia receiving risperidone were recently released. The overall risk of cerebrovascular adverse events was 4% in the risperidone-treated group compared to 2% in the placebo group; four patients died in the risperidone group vs. one patient in the placebo group. A further search of postmarketing databases

revealed 37 cases of cerebrovascular adverse events in elderly dementia patients taking risperidone, of which 16 (43%) were fatal.

The manufacturer of risperidone recently stated that it intends to send letters to U.S. physicians advising them of the possibility of increased risk of stroke among elderly patients taking risperidone and to make changes to product labeling more clearly outlining available information about risk in elderly patients. A similar warning was released in Canada last October, with a summary and review of available information published in the November 2002 issue of the Canadian Medical Association Journal (Wooltorton, 2002). The Canadian letter to physicians is available at: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/risperdal1_e.pdf.

Whether other atypical antipsychotic agents are associated with similar cerebrovascular risks is unknown.

- *Prolactin elevation* - Blockade of D2 receptors in the hypothalamus can result in increased prolactin secretion, which can lead to breast swelling, tenderness, and discharge; menstrual cycle irregularity or amenorrhea; sexual dysfunction; anovulation; and osteoporosis. Elevated prolactin levels do not always correlate with the presence of symptoms; long-term consequences of elevated prolactin are unclear. Atypical antipsychotics have a lower risk for causing prolactin elevation than typical antipsychotics, due to selectivity in the limbic system and higher 5-HT2 to D2 binding ratios. Of the atypical antipsychotics, risperidone has been associated with the largest increases in prolactin levels.
- *Other adverse effects* considered by the Council included the risk of orthostatic hypotension, anticholinergic effects, somnolence, cataracts, sexual dysfunction, priapism, and seizure.

Cost

MTFs spent about $11.3 million on atypical antipsychotics in FY 02: $5.6M for olanzapine, $3.8M for risperidone, $1.4M for quetiapine, $0.4M for ziprasidone, and $0.1M for clozapine. The average cost per day (tabs/caps only) is given in Table 3 below:

Table 3 - Average cost per tab/cap, tab/caps per day, and average cost per day for atypical antipsychotics in MTFs

	Average cost per tab/cap (PV data Dec 02-Feb 03)	Average tabs/caps per day** (PDTS data Jan 03-Mar 03)	Average cost per day
Aripiprazole*	$7.13	1.01	$7.21
Olanzapine	$4.22	1.33	$5.61
Quetiapine	$1.23	2.14	$2.64
Risperidone	$1.88	1.60	$3.01
Ziprasidone	$2.32	1.97	$4.56

* Limited data for aripiprazole
** Based on days supply. Results are consistent with those calculated for the retail network and mail order and with an older analysis based on directions for use.

The Council considered BPAs or incentive purchase agreement offers from the manufacturers of olanzapine, quetiapine, and risperidone. Offers differed considerably regarding the basis for price discounts and the considerations required by the manufacturers. A cost impact analysis by LCDR Ted Briski showed that annual cost avoidance ranging from $0.7 million to $1 million (based on current usage) could be attained by accepting two of the three offers.

After weighing relative usage, clinical factors, and economic factors, the Council voted to add risperidone and quetiapine to the BCF. The Council noted the following:

- Risperidone is by far the most commonly used atypical antipsychotic in the pediatric population, an age group in which use of this drug class is relatively high. Ensuring uniform availability of this agent across the system may benefit military personnel with children, who commonly move from MTF to MTF.
- The recent reports of an increased incidence of stroke in elderly patients with dementia receiving risperidone may lead to preferential use of other atypical antipsychotics in elderly patients (although there are no data indicating whether the same effect occurs with other atypical antipsychotics). Taken along with the general inter-patient variability in this drug class and the higher incidence of EPS and prolactin elevation with risperidone, this argues for the presence of a second agent on the BCF.
- Data for differences in efficacy among the various agents are not compelling, particularly considering the likelihood of use in conditions other than schizophrenia. However, adverse effect profiles differ considerably. All of the most commonly used medications have adverse effect concerns. Data on the newer agents, ziprasidone and aripiprazole, which may avoid some common adverse affects, are limited, and usage is low.
- Quetiapine and risperidone are the least costly agents on a cost per day basis.
- MTFs are free to add or retain additional atypical antipsychotics on their formularies if required locally.

C. *Topical Immunomodulators (TIMS)*

In November 2002, the DoD P&T Executive Council agreed that TIMS are a unique class and have a substantial place in therapy for the treatment of atopic dermatitis (AD), however there was concern regarding the cost of these agents and the potential for overuse. The Council agreed to consider one or both of these medications for addition to the BCF after procurement options were explored.

Efficacy – Randomized controlled clinical trials demonstrate that both agents are more efficacious than placebo in the treatment of AD. Tacrolimus, an ointment, appears to be as efficacious as a medium potency topical corticosteroid (TCS) whereas pimecrolimus, a cream, is as efficacious as a low potency TCS. Tacrolimus is indicated for moderate to severe AD while pimecrolimus is indicated for mild to moderate AD. Ninety percent of patients have mild to moderate AD and the rest are moderate to severe. Most of the use is in the very young (ages 0-4) and elderly (ages 65+).

Safety/Tolerability – Neither drug has clinically significant adverse effects that cause the patients to discontinue use. The drugs are not systemically absorbed, so they can be used long term without potential problems associated with long-term TCS use. TIMS can also be used on sensitive body areas such as the face and intertriginous regions where one would not want to use a TCS. Because pimecrolimus is a cream and less occlusive, it is preferred over tacrolimus for areas like the face, perioribital eyelids, and flexural and groin areas.

Other – Provider response was markedly positive regarding the prospect of having an alternative to TCSs on MTF formularies. At the same time, providers noted that these would not take the place of the low potency TCSs or other initial therapies for mild AD. Of 68 provider responses, 60 recommended adding one or both agents to the BCF. Of these 60 responses, 33 preferred pimecrolimus, 6 preferred tacrolimus, and the rest either had no preference or wanted both agents on the BCF. Pimecrolimus prescription fills are increasing at all points of service (MTF, TMOP, and retail). Pimecrolimus is currently on 49 percent of all MTF formularies. Tacrolimus is on 25 percent of MTF formularies; tacrolimus prescription fills for all points of service have leveled off at a point well below pimecrolimus.

Cost – Novartis offered an incentive agreement contingent on pimecrolimus being added to the BCF. The agreement provides a discount on all future purchases.

The Council voted unanimously to add pimecrolimus to the BCF. After being reviewed by dermatologists, a place in therapy (PIT) guide will be disseminated to the MTFs as a tool to help reduce potential inappropriate use.

8. REQUESTS FOR BCF CHANGES

A. *Nitroglycerin Products on the BCF*

The American College of Cardiology/American Heart Association currently considers nitroglycerin as third-line treatment for *chronic* symptoms of angina. Despite this third-line consideration for use, nitroglycerin transdermal systems currently account for approximately 8,000 prescriptions monthly in the MHS, second only to the sublingual tablets (approximately 15,000 prescriptions/month). Other nitroglycerin preparations (translingual spray, sustained release capsules, and ointment) combined account for approximately 6,000 prescriptions/month. Current BCF nitroglycerin products include sublingual nitroglycerin tablets, translingual spray, and isosorbide dinitrate oral. The BCF does not contain a long acting nitroglycerin product.

Transdermal nitroglycerin systems are on 75% (86/114) of local MTF formularies. A DoD/VA joint contract for nitroglycerin transdermal systems from Schering provides the patches at a cost of $0.16/day ($4.89/month).

An analysis of MHS prescription data revealed a steadily increasing number of prescriptions for isosorbide mononitrate oral for all three points of service in the MHS (approximately 16,000 prescriptions/month combined). Isosorbide mononitrate oral is on 43% (49/114) of local MTF formularies. The DoD/VA currently has a joint contract for a generic once daily isosorbide mononitrate oral tablet at a cost ranging between $0.04 to $0.06/day, depending on strength.

The Council voted unanimously to add the contracted nitroglycerin transdermal system and the contracted once daily preparation of isosorbide mononitrate oral to the BCF, due to wide usage in the MHS and low cost.

B. *Administrative Changes Concerning the Process for Requests from the Field for BCF Changes*

In order for the PEC to provide support materials for agenda items to the Council members three weeks prior to the meeting, a deadline needs to be established for submission or requests for BCF changes. To allow sufficient time to complete an analysis and prepare a recommendation for any submitted request, the PEC recommended that the deadline for BCF change requests should be 6 weeks prior to the next regularly scheduled meeting. The Executive Council concurred with this recommendation.

A second issue concerned the potential need for individuals requesting the addition of an agent to the BCF to disclose whether they have a financial interest or other relationship with the manufacturer of the product that could be perceived as a conflict of interest. The purpose of this disclosure would not be to prevent the consideration of the request, but to provide the Council with information that would allow it to make a more informed and credible decision. It was initially proposed that a disclosure form should be required to accompany a request for a BCF change. Some Council members suggested that if disclosure forms are required for BCF change requests, the same type of disclosure should be required for input regarding other P&T actions. Council members were concerned that the paperwork burden would degrade the ability of the PEC to obtain input from providers. The Council voted to table this issue and tasked the PEC to clarify the necessary scope and process for obtaining disclosure statements on any input related to formulary decisions making. The PEC is to present a revised recommendation at the next meeting.

9. ADJOURNMENT

The meeting adjourned at 1500 hours. The next meeting will be held at TRICARE Management Activity (TMA), conference room 815, Skyline Building 6, 5111 Leesburg Pike, Falls Church, VA at 0800 on Tuesday, 5 August 2003. All agenda items should be submitted to the co-chairs no later than 18 July 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **6 MARCH 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 6 March 2003, at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (for COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Mike Valentino	Department of Veterans Affairs
Dr. Trevor Rabie	Uniformed Services Family Health Plan
COL Doreen Lounsbery, MC	Army

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
COL Mike Heath, MS	Army Pharmacy Consultant, Chairman Pharmacy Board of Directors
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
David Chicoine	Uniformed Services Family Health Plan
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
LtCol Dave Bennett, USAF, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, USAF, MC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
Mark Hughes	Express Scripts
MAJ John Howe, MS	Defense Supply Center Philadelphia
Kathy Tortorice	Department of Veterans Affairs
Shannon Rogers	Humana
William Hudson	Humana
Gene Lakey	TriWest
Ray Nan Berry (via T-Con)	Health Net Federal Services
Ron McDonald (via T-Con)	Sierra

3. **REVIEW MINUTES OF LAST MEETING** – The minutes from the last meeting were accepted as written.

4. **INTERIM/ ADMINISTRATIVE DECISIONS** – Trovafloxacin was excluded from the NMOP/TMOP since its use is reserved for "patients with serious, life- or limb-threatening infections who receive their initial therapy in an inpatient health care facility," and is restricted to a two-week period.

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL William Davies, DoD Pharmacy Program Director, TMA, stated that the responses to the public comments on the proposed rule are nearly finalized and will undergo a legal review.

6. **BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES** – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 6 new drugs or formulations (see Appendix A). The PEC also presented brief information on fourteen additional new drugs or formulations not requiring a complete review by the Committee (see Appendix B). The Committee agreed that no further review was required.

7. MAIL ORDER AND RETAIL NETWORK ISSUES

A. *Implementation of the TMOP on 1 March 2003* - COL Davies (TMA) and Lisa LeGette from Express Scripts (the contractor for the TMOP program) provided an overview of the implementation of the TRICARE Mail Order Pharmacy program, and the progress of the changeover from the previous National Mail Order Pharmacy (NMOP) program. Shana Trice (PEC) reviewed the new TMOP Formulary page on the PEC website and explained changes from the old NMOP Formulary page. She also discussed revisions to the DoD Quantity Limits page to better reflect implementation of the quantity limits at the TMOP.

The URL for the TMOP Formulary page is: www.pec.ha.osd.mil/TMOP/TMOPhome.htm. Comprehensive benefit information for the TMOP may be found on the TRICARE website at: http://www.tricare.osd.mil/pharmacy/tmop.cfm, while the Express-Scripts website (www.express-scripts.com; click on the DoD seal) provides beneficiaries with the ability to register for the TMOP online, download registration forms, order refills, check order status, etc.

B. *New "line extension" rule for the TMOP* – The Council agreed that newly approved combination products involving addition of a diuretic to another antihypertensive medication may be automatically added to the TMOP Formulary as a line extension, pending confirmation by the Committee at the next scheduled meeting. The Committee asked for a review of "line extension rules" for the TMOP at the next meeting in May 2003. The rules currently in effect are those previously approved for the NMOP; however, there are operational differences between the two programs that affect the manner in which the rules are applied.

8. PRIOR AUTHORIZATIONS (PAs)

The Committee approved prior authorization criteria for adalimumab (Humira) and modifications to prior authorization criteria for etanercept (Enbrel) and anakinra (Kineret) (see Appendix D).

9. CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS – Buprenorphine & buprenorphine/naloxone (Subutex/Suboxone) are subject to a controlled distribution process, but it is not clear to the Committee that these medications are covered under TRICARE rules. Enfuvirtide (Fuzeon) a new HIV medication will be manufactured on a limited scale, however the distribution process is unknown. Further information on both these products should be available by the next meeting. Peginterferon-alfa 2b (PEG-Intron) and etanercept (Enbrel) are no longer under controlled distribution.

10. ADJOURNMENT – The meeting adjourned at 1130 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Wednesday, 7 May 2003. All agenda items should be submitted to the co-chairs no later than 18 April 2003.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE TRICARE MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Nitazoxanide 100 mg/5 mL oral suspension (Alinia; Romark Labs)	22 Nov 02: Treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*, in pediatric patients 1 through 11 years of age. Nitazoxanide is given every 12 hours for 3 days. Nitazoxanide is the first anti-parasitic product approved specifically for treating cryptosporidiosis and the only drug approved for treatment of giardiasis in ages 1-11 years that is available in a suspension formulation. A tablet formulation of nitazoxanide for adults with intestinal parasites is "approvable" at the FDA.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization:** None	Not added to the BCF **Similar BCF agents:** Metronidazole oral tablets; requires extemporaneous compounding to make a suspension.
Eletriptan tablets (Relpax; Pfizer)	26 Dec 02: Indicated for the acute treatment of migraine attacks with and without aura in adults. This is the 7th 5-HT receptor agonist (triptan) marketed.	Added to the TMOP Formulary	**Quantity Limits** Quantity limits exist for other triptans. Packaged in 12's. **Retail**: 12 tablets/30 days" **TMOP:** 36 tablets/90 days **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** sumatriptan oral tablets and auto-injector. **Note:** A contracting initiative for the triptan class is underway.
Aripiprazole tablets (Abilify; BMS)	15 Nov 02: Atypical antipsychotic indicated for the treatment of schizophrenia. Unlike other atypical antipsychotics, aripiprazole functions as a partial agonist at dopamine D_2 receptors; the clinical significance of this difference is unknown.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None **Note:** Addition of one or more atypical antipsychotics to the BCF is under discussion.
Teriparitide (rDNA origin) injection (Forteo; Lilly)	26 Nov 02: Recombinant parathyroid hormone (PTH); stimulates new bone formation by increasing osteoblast activity. Teriparitide is indicated for the treatment of men and postmenopausal women with osteoporosis who are at high risk for fracture, including those with a history of osteoporotic fracture, multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy. Once-daily subcutaneous administration; may be self-injected. The injection device is similar to Lilly's insulin pen. Requires refrigeration. Black box warning for osteosarcoma in rodent studies. Patient medication guide must be dispensed with the product.	Added to the TMOP Formulary & TMOP Covered Injectables List	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Alendronate tablets are on the BCF. Potential contracting initiative for alendronate or risedronate is under consideration.

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Atomoxetine capsules (Strattera; Lilly)	26 Nov 02: Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children (down to age 6 years). Atomoxetine is a highly selective norepinephrine re-uptake inhibitor. It is the only non-controlled medication approved for the treatment of ADHD and the only medication approved for the treatment of ADHD in adults.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Existing products for ADHD are all Schedule II controlled substances: methylphenidate ER (specific brand is Concerta); methylphenidate IR; D,L amphetamine ER (Adderall XR).
Adalimumab injection (Humira; Abbott)	2 Jan 03: Monoclonal antibody that binds to tumor necrosis factor (TNF) alpha. Indicated for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active RA who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Can be used alone or in combination with methotrexate. Administered as a single dose 40 mg subcutaneous (SQ) injection every two weeks (patients not on methotrexate may require weekly administration). May be self-injected. Other similar biologics – etanercept, and infliximab, both TNF inhibitors, and anakinra, an interleukin-1 inhibitor – are also indicated for RA. Etanercept is also indicated for juvenile RA and psoriatic arthritis; infliximab for Crohn's disease. Etanercept (Enbrel) is administered SQ twice a week; infliximab (Remicade) as a monthly IV infusion, and anakinra (Kineret) as a daily SQ injection. Adalimumab contains the same black box warnings as other TNF blockers for emergence of serious infections during treatment, including disseminated or extrapulmonary tuberculosis.	Added to the TMOP Formulary & Covered Injectables List	**Quantity Limits** **TMOP**: 6 syringes per 6 weeks (3 packs of 2 syringes) **Retail:** 4 syringes per 4 weeks (2 packs of 2 syringes) **Note**: the quantity limits allow for the possibility of once weekly administration of adalimumab in some patients. Quantity limits are in place for both etanercept and anakinra. **Prior Authorization** ▪ Yes. See Appendix D for criteria.	Not added to the BCF **Similar BCF agents**: none

APPENDIX B: NEWLY APPROVED DRUGS NOT REQUIRING FULL REVIEW BY THE P&T COMMITTEE

Generic name (Trade name; manufacturer)	**Comments**
Isotretinoin capsules (Amnesteem; Bertek); (Sotret; Ranbaxy)	AB rated generics to Accutane (Roche brand of isotretinoin). Isotretinoin is excluded from the TMOP Formulary.
Ciprofloxacin extended-release tablets (Cipro XR; Bayer)	Approved for uncomplicated UTI caused *by E. coli*, *Proteus*, *Enterococcus*, and *Staphylococcus*; 3-day regimen. Automatically added to TMOP Formulary as a line extension. Ciprofloxacin is not on the BCF.
Stavudine extended release capsules (Zerit XR; BMS)	Nucleoside reverse transcriptase inhibitor for HIV. Automatically added to TMOP Formulary as a line extension. Stavudine is not on the BCF.
Alprazolam extended release capsules (Xanax XR; Pharmacia)	Approved for panic disorder. Automatically added to TMOP Formulary as a line extension. Alprazolam is not on the BCF.
Alpha-1 proteinase inhibitor, human injection (Aralast; Baxter/Alpha)	Orphan drug for hereditary emphysema/alpha 1 antitrypsin deficiency. Requires IV infusion. Not considered for the TMOP Covered Injectables List since it is not designed for self-administration. Not considered for the BCF due to the specialized nature of the indication.
Testosterone gel 1% topical (Testim; Auxilium Pharmaceuticals)	Approved for treatment of primary hypogonadism; 2nd testosterone gel on the market. Not generically substitutable for Androgel; both are reference listed drugs. Automatically added to TMOP Formulary as a line extension. Schedule III controlled medication. Although the general rule limits controlled medications to a 30-day supply at the TMOP, Testim falls under an already established exception to this rule that provides for up to a 90-day supply at the TMOP for commercially available topical testosterone products. Testosterone gel is not on the BCF.
Azelaic acid gel 15% topical (Finacea; Berlex)	Approved for mild to moderate rosacea. A similar product, azelaic acid 20% cream (Fineven; Berlex), approved for acne, is already available from the TMOP. Automatically added to TMOP Formulary as a line extension. Azelaic acid products are not on the BCF.
70% insulin aspart protamine suspension/30% insulin aspart injection (Novolog Mix 70/30 vials & pens; Novo Nordisk)	Biphasic insulin produced by adding protamine to Novolog. Automatically added to TMOP Formulary as a line extension.
Insulin aspart injection (Novolog flex pen; Novo Nordisk)	New packaging for insulin aspart. Automatically added to TMOP Formulary as a line extension.
Alefacept injection (Amevive; Biogen)	Biologic for moderate to severe plaque psoriasis given as a weekly IV bolus or IM injection. Not considered for the TMOP Covered Injectables List since it is not designed for self-administration. Not considered for the BCF due to the specialized nature of the indication.
Ribavirin capsules (Copegus; Roche)	Roche brand of ribavirin for use in combination with pegylated interferon. The Schering brand of ribavirin (Rebetol) is already available from the TMOP. Automatically added to TMOP Formulary as a line extension. Ribavirin is not on the BCF.
Diltiazem graded release tablet (Cardizem LA; Biovail)	New controlled release once-daily formulation of diltiazem; may be dosed in the morning or at bedtime. Not generically substitutable for Cardizem CD or Tiazac. Anticipated availability April 2003. Automatically added to TMOP Formulary as a line extension. Tiazac is the BCF selection for a once-daily diltiazem product.
Cyclobenzaprine tablets (Flexeril; McNeil)	New lower 5 mg dosage form. Automatically added to TMOP Formulary as a line extension. Cyclobenzaprine is not on the BCF.
Eprosartan/HCTZ tablets (Teveten HCT; GSK)	New combination of an angiotensin receptor blocker with hydrochlorothiazide. Automatically added to TMOP Formulary as a line extension. A VA/DoD solicitation for angiotensin receptor blockers is in progress.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. *Additions to the BCF*

      1) Chlorthalidone
      2) Benztropine
      3) Trihexyphenidyl
      4) Amantadine
      5) Lansoprazole
      6) Goserelin (Zoladex) 1- and 3-month products for the treatment of prostate cancer

   B. *Deletions, changes, clarifications or exclusions from the BCF* - None

2. **TMOP FORMULARY CHANGES**

   A. *Additions to the TMOP Formulary*

      1) Nitazoxanide oral suspension (Alinia; Romark Labs)
      2) Eletriptan tablets (Relpax; Pfizer) – quantity limits apply, see below
      3) Aripiprazole tablets (Abilify; BMS)
      4) Teriparitide (rDNA origin) injection (Forteo; Lilly) – added to the TMOP Covered Injectables List
      5) Atomoxetine capsules (Strattera; Lilly)
      6) Adalimumab injection (Humira; Abbott) – added to the TMOP Covered Injectables List with prior authorization criteria; quantity limits apply, see below

   B. *Exclusions from the TMOP Formulary*

      1) Trovafloxacin (Trovan; Pfizer) – specifically excluded from the TMOP Formulary, since its use is reserved for "patients with serious, life- or limb-threatening infections who receive their initial therapy in an inpatient health care facility," and is restricted to a two-week period.

   C. *Deletions, changes, or clarifications to the TMOP Formulary* - None

3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**

   A. Quantity limit for eletriptan tablets (Relpax; Pfizer): 12 tablets (1 pack) per 30-day supply (retail); 36 tablets (3 packs) per 90-day supply (TMOP); consistent with existing quantity limits for other triptans (within limitations of package size)

   B. Quantity limit for adalimumab injection (Humira; Abbott): 4 syringes (2 packs of 2 syringes) per 4 weeks (retail); 6 syringes (3 packs of 2 syringes) per 6 weeks (TMOP)

4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION PROGRAM**

   A. Prior authorization criteria established for adalimumab injection (Humira; Abbott) – see Appendix D

   B. Prior authorization criteria for etanercept and anakinra modified – see Appendix D

APPENDIX D: PRIOR AUTHORIZATION CRITERIA FOR ADALIMUMAB (HUMIRA) & CHANGES TO PRIOR AUTHORIZATION CRITERIA FOR ETANERCEPT (ENBREL) AND ANAKINRA (KINERET)

Drug	FDA Indications	New TMOP Prior Authorization Criteria
Adalimumab (Humira)	• Reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.	• Coverage provided for the treatment of moderately to severely active rheumatoid arthritis in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD). • Coverage NOT provided for concomitant use with anakinra (Kineret), etanercept (Enbrel), or infliximab (Remicade).
Anakinra (Kineret)	• Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs).	• Coverage provided for the treatment of moderately to severely active rheumatoid arthritis in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD). • Coverage NOT provided for concomitant use with adalimumab (Humira), etanercept (Enbrel) or infliximab (Remicade). *Changes to previous criteria:* • Listing adalimumab, etanercept, and infliximab as DMARDs. • Adding adalimumab to the statement: "Coverage NOT provided for concomitant use with etanercept (Enbrel) or infliximab (Remicade)." • Making criteria more consistent with package labeling and with criteria for adalimumab by changing the previous requirement that the patient fail (or be unable to take) MTX AND fail at least one other DMARD.
Etanercept (Enbrel)	• Reducing signs and symptoms and inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis. • Reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. • Reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.	• Coverage provided for the treatment of moderately to severely active rheumatoid arthritis OR active psoriatic arthritis. • Coverage provided for the treatment of juvenile rheumatoid arthritis when the patient has an inadequate response to at least one disease-modifying antirheumatic drug (DMARD). • Coverage NOT provided for concomitant use with adalimumab (Humira), anakinra (Kineret), or infliximab (Remicade). *Changes to previous criteria:* • Listing adalimumab, anakinra, and infliximab as DMARDs. • Adding the provision that coverage is not provided for concomitant use with adalimumab, anakinra, or infliximab.

For all three prior authorizations:

The following are examples of DMARDs:

- o adalimumab
- o anakinra
- o etanercept
- o infliximab
- o azathioprine
- o hydroxychloroquine
- o gold compounds, oral/injectable (e.g., auranofin, aurothioglucose, gold sodium thiomalate)
- o leflunomide
- o methotrexate
- o d-penicillamine
- o sulfasalazine

Department of Defense
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MCCS-GPE **5 March 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 5 March 2003 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Mike Valentino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath, MS	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
MAJ John Howe, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Kathy Tortorice	Department of Veterans Affairs, PBM
Capt Cherie-Anne Mauntel, BSC	USAF AFIT Student
CPT Tamba Dauda, MS	Pharmacy Resident, WHMC/BAMC
Capt Glenn L. Laird, BSC	Pharmacy Resident, WHMC/BAMC
Capt Agnes Kim, BSC	Pharmacy Resident, WHMC/BAMC
CPT Larry Ricks, MS	Pharmacy Resident, WHMC/BAMC

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. ADMINISTRATIVE ISSUES

A. *Membership and Meeting Frequency*: The Council discussed potential changes in its membership and the need to conduct additional Council meetings via teleconference in order to make timely decisions regarding joint VA/DoD pharmaceutical procurement strategies. The Council concluded that the charter that governs the DoD P&T Committee and Executive Council should be revised. COL Remund will develop an initial draft of a new charter.

The Council welcomed new members COL Doreen Lounsbery and CDR Mark Richerson, taking the place as voting members for COL Rosa Stith and CDR Kevin Cook, respectively.

B. *Clinical Reviews:* A Clinical Workgroup comprised of three members each from the VA PBM and the PEC are working to integrate and standardize the processes for completing clinical reviews of drug classes and drug monographs for new molecular entities.

C. *Rx NET:* RxNET is a web forum that the PEC established to facilitate communication among health care professionals involved in the delivery and management of drug therapy in the Military Health System. Dave Bretzke serves

as the administrator for RxNET. Council members are encouraged to use the forum that has been established for the DoD P&T Council within RxNET.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARD, RENEWALS AND TERMINATIONS

A. New joint DoD/VA contracts were awarded for permethrin cream (West-ward), tretinoin topical cream (Allergan), and colchicine tablets (West-ward).

B. Joint DoD/VA contracts for erythromycin topical and clindamycin topical were not awarded because the bid prices were higher than existing FSS prices. The hydrochlorothiazide/triamterene joint contract was not awarded due to lack of offers.

C. New joint DoD/VA blanket purchase agreements were awarded for fluticasone (Flonase; Pharmacia), nisoldipine (Sular; 1st Horizon), tolterodine tartrate extended release capsules (Detrol LA; Pharmacia), lansoprazole (Prevacid; TAP), rabeprazole (Aciphex; Janssen), and levothyroxine (Synthroid; Abbott).

6. PROCUREMENT INITIATIVES

A. The following joint DoD/VA contracts are in various stages of solicitation: isosorbide dinitrate, ketoconazole cream, midazolam injectable, pamidronate injectable, and tramadol tablets.

B. A joint DoD/VA solicitation for a "triptan" closed 20 Dec 02, but the solicitation has been protested to the General Accounting Office (GAO).

C. A joint DoD/VA solicitation for bisphosphonates is being developed. A projected issue date is not yet identified.

D. A joint DoD/VA solicitation for angiotensin receptor blockers (ARBs) has been drafted and is currently being reviewed and edited.

E. A joint DoD/VA solicitation for a thiazolidinedione is being developed. A projected issue date is not yet identified.

F. Levothyroxine (Synthroid) – The price for the Synthroid brand of levothyroxine recently increased from $0.02 per tablet to $0.07 per tablet. In light of the price increase, the Council considered the possibility of a contracting action that would compete various levothyroxine products. Synthroid accounts for 97% of the levothyroxine market at MTF pharmacies. None of the levothyroxine tablets marketed by other companies are "A-rated" to Synthroid. A contracting action that caused patients to be switched from Synthroid to another levothyroxine product would result in therapeutic substitutions requiring additional laboratory tests to monitor thyroid levels. The Council unanimously voted not to pursue a contract for a single levothyroxine product on the BCF.

G. Statins – A joint DoD/VA solicitation for a high potency statin closed 28 February 2003. The solicitation permits (but does not mandate) the addition of generic lovastatin and/or a non-CYP3A4 metabolized statin (pravastatin or fluvastatin) to the BCF. Lovastatin, pravastatin and fluvastatin have not been on

any MTF formularies since the current closed class statin contract was awarded in August 1999.

1) Lovastatin accounts for less than 1% of statin usage at MTFs. Lovastatin costs $0.26 per tablet (joint VA/DoD contract price), so it does not offer any price advantage compared to the current contract prices for the strengths of simvastatin that achieve similar reductions in LDL-cholesterol. The future contract prices for a high potency statin are expected to be even lower. The Council voted to not add lovastatin to the BCF. Individual MTFs may add lovastatin to their local formularies if they determine there is a need to do so.

2) Pravastatin and fluvastatin together account for less than 1% of MTF statin usage. Pravastatin and fluvastatin prices are higher than the contract prices for the strengths of simvastatin that achieve similar reductions in LDL-cholesterol. Since pravastatin and fluvastatin do not offer an economic advantage, their use should be limited to patients who have a clinical need for a non-CYP3A4-metabolized statin. If pravastatin or fluvastatin were added to the BCF, MTFs would no longer be able to use the non-formulary request process to limit usage to patients who have a specific clinical need for these agents. The Council voted to not add a non-CYP3A4 metabolized statin to the BCF and also to not participate in any contracting initiative that would require addition of pravastatin or fluvastatin to the BCF. Individual MTFs may add either pravastatin or fluvastatin to their local formularies if they determine there is a need to do so.

H. LHRH Agonists – The Council voted to add goserelin acetate (Zoladex) 3.6 mg and 10.8 mg implants to the BCF for the treatment of prostate cancer based on a joint DoD/VA contract that was awarded to Astra Zeneca. The contract specifies that Zoladex is the sole LHRH agonist on the Basic Core Formulary (BCF) **for the treatment of prostate cancer**, and that other LHRH agonist dosage forms used for prostate cancer are not allowed on MTF formularies. MTFs are allowed to have additional LHRH agonist products on their formularies for the treatment of conditions other than prostate cancer. Detailed guidance regarding the Zoladex contract is on the PEC website at:

http://www.pec.ha.osd.mil/Contracts/LHRH_Agonist_Contract_Guidance.htm

I. Prostaglandins – The Council voted at the November 2002 meeting to add a prostaglandin to the BCF utilizing a closed class contracting strategy competing latanoprost, bimatoprost and travoprost, which would not require patients to be switched from one agent to another. The ophthalmology consultants for the three services subsequently expressed disagreement with the Council's decision. The consultants' concerns centered on (1) evidence from clinical trials and clinical experience that bimatoprost and travoprost have a higher incidence of hyperemia than latanoprost and (2) less certainty regarding the safety of bimatoprost and travoprost because they have been on the market for less time than latanoprost.

The Council reviewed safety and tolerability data from clinical trials of ophthalmic prostaglandins, data on adverse effects and discontinuation rates from a phase IV study of bimatoprost, VA and DoD usage data, and information about

a switch from latanoprost to bimatoprost by a Kaiser health plan. After a lengthy discussion the Council passed a motion (by an 8 to 3 vote) to reaffirm its decision to seek a contract for a single ophthalmic prostaglandin. Members voting in favor of the motion tended to agree with the argument that differences in the incidence of hyperemia were unlikely to lead to clinical problems of a magnitude that would make bimatoprost or travoprost an unacceptable choice as the sole ophthalmic prostaglandin on the BCF. Members voting in favor of the motion also acknowledged that the longer a drug is on the market the more we generally know about its safety profile, but they concluded that selection of any of the ophthalmic prostaglandins as the sole agent on the BCF would not pose an unacceptable safety risk.

J. Proton Pump Inhibitors (PPIs) – In December 2002 Janssen communicated that Eisai, the manufacturer of rabeprazole (Aciphex), had decided to raise the price of rabeprazole (Aciphex) to the DoD and VA from $0.22 per unit to $0.35 per unit on 1 January 2003, and then to approximately $1.90 per unit on 1 April 2003. The impending price increases caused DoD and the VA to negotiate vigorously with all manufacturers of branded PPIs. Three of the four current manufacturers of branded PPIs submitted proposals to the DoD and VA.

The Council voted unanimously to accept blanket purchase agreements offered by Eisai/Janssen for Aciphex and TAP Pharmaceuticals for lansoprazole (Prevacid). Aciphex will remain on the BCF, and Prevacid will be added to the BCF.

7. Place In Therapy (PIT) Recommendations – PIT recommendations are intended to aid practitioners in the appropriate use of selected medications. The Council reviewed and accepted the revised PIT recommendations for angiotensin II receptor blocker (ARBs). The ARB PIT recommendations will be disseminated to MTFs.

The PEC is developing PIT recommendations for topical immunomodulators (TIMS) and overactive bladder (OAB). The draft PIT recommendations will be disseminated to Council members through RxNET or email. Council members will have a 10-day period to review and comment. The PEC will then modify the PIT recommendations as necessary and disseminate them to MTFs.

8. FORMULARY DECISION FOLLOW-UP

A. *Evista* — Evista was added to the BCF in May 2002. The PEC analyzed prescription data from PDTS to determine the extent to which patients who obtained Evista from retail pharmacies before it was added to the BCF subsequently obtained Evista from MTF pharmacies. An analysis of 11,108 patients who obtained Evista from retail network pharmacies between 1 March 2002 and 1 June 2002 showed that:

- 864 patients (8%) subsequently obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002
- 10,244 patients (92%) continued to obtain Evista only from retail network pharmacies between 1 September 2002 and 6 December 2002

The PEC repeated the analysis after dividing the 11,108 patients into two groups. Group 1 included 3,092 patients who obtained prescriptions for drugs other than Evista from MTF pharmacies between 1 March 2002 and 1 June 2002. Group 2 included 8,016 patients who obtained prescriptions for drugs other than Evista at retail network pharmacies only between 1 March 2002 and 1 June 2002. The analysis showed that:

- 693 (22%) of the patients in Group 1 obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002
- 171 (2%) of the patients in Group 2 obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002

B. *Advair* — Advair was added to the BCF February 2002. The PEC analyzed prescription data from PDTS to determine the extent to which patients who obtained Advair from retail pharmacies before it was added to the BCF subsequently obtained Advair from MTF pharmacies. An analysis of 9,853 patients who obtained Advair from retail network pharmacies between 1 December 2001 and 1 March 2002 showed that:

- 1,874 patients (19%) subsequently obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003
- 7,979 patients (81%) continued to obtain Advair only from retail network pharmacies between 1 June 2002 and 20 February 2003

The PEC repeated the analysis after dividing the 9,853 patients into two groups. Group 1 included 2,838 patients who obtained prescriptions for drugs other than Advair from MTF pharmacies between 1 December 2001 and 1 March 2002. Group 2 included 7,015 patients who obtained prescriptions for drugs obtained at retail network pharmacies only between 1 December 2001 and 1 March 2002. The analysis showed that:

- 1,457 (51%) of the patients in Group 1 obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003
- 417 (6%) of the patients in Group 2 obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003

9. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES:

A. *Cholinesterase Inhibitors* — Cholinesterase inhibitors are the primary treatment for cognitive symptoms and functional disability of Alzheimer's disease (AD). Four cholinesterase inhibitors are currently available in the United States: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). The VA plans to conduct a clinical review of the class to determine potential contracting opportunities. The BCF does not include a cholinesterase inhibitor. CDR Graham presented a brief overview of cholinesterase inhibitors to assist the Council in deciding whether or not a cholinesterase inhibitor should be added to the BCF.

Efficacy: Cholinesterase inhibitors have been shown to delay neuropsychiatric, cognitive and functional decline in patients with mild to moderate AD. Long-term studies on outcomes such as patient quality of life, institutionalization, and caregiver burden have not been conducted, but short-term trials have shown that cholinesterase inhibitors delay nursing home placement and reduce costs of care in the home.

Safety/Tolerability: Generally the agents are well tolerated with common adverse effects managed with titration and dose adjustments. Common adverse effects are related to excessive cholinergic activity consisting of nausea, diarrhea, vomiting, and occasionally excessively vivid dreaming. Tacrine (Cognex) use has been limited due to associated risks of hepatotoxicity.

Other factors: The following table displays FSS cost of cholinesterase inhibitors.

	Tacrine	Donepezil	Rivastigmine	Galantamine
FSS Price/Unit	$0.80/cap	$2.54/tab	$1.30/tab	$1.30/tab
Dosage Frequency	QID	QD	BID	BID
Cost/day	$3.20/day	$2.54/day	$2.60/day	$2.60/day
Cost/month	$96.00/month	$76.20/month	$78.00/month	$78.00/month

PDTS data from October 2002 to January 2003 show that donepezil (Aricept) has the majority of the DoD market share in all three points of service, with a steady increase in prescription fills for donepezil, rivastigmine, and galantamine in all three points of service. MTFs are currently spending nearly $100,000 per month on cholinesterase inhibitors.

A Council member expressed the opinion that the cholinesterase inhibitors are very expensive compared to the relatively modest clinical benefits they offer. The Council voted 10 to 1 not to consider the addition of a cholinesterase inhibitor to the BCF.

B. *Parkinson's Disease*

Carbidopa/ levodopa immediate release (Sinemet IR) formulation is currently the only drug on the BCF for the treatment of Parkinson's disease. The Council addressed the following questions:

- Should carbidopa/levodopa controlled release (Sinemet CR) be added to the BCF or replace carbidopa/levodopa immediate release on the BCF?
- Should adjunctive therapy agents (anticholinergic agents and amantadine) be added to the BCF?
- Should one or more of the dopamine agonists (bromocriptine, pergolide, pramipexole, ropinirole) be added to the BCF?

Carbidopa/levodopa controlled release: Carbidopa/levodopa is the most effective drug for the symptomatic treatment of idiopathic Parkinson's disease. There is no

evidence of a clinical advantage for the controlled release (CR) form of carbidopa/levodopa compared to the immediate release (IR). The daily cost of therapy with the CR is substantially higher, ranging from $1.00 to $2.50 vs $0.20 to $0.80 for the immediate release (IR). The Council unanimously voted to not add carbidopa/levodopa CR to the BCF.

Adjunctive therapy: Adjunctive treatment for Parkinson's disease includes anticholinergic agents (trihexyphenidyl, benztropine) and amantadine. Adjunctive therapy agents are effective monotherapy treatment for tremors in patients under the age of 70 in whom akinesia is not a significant problem. Additionally, they may be useful in patients with more advanced disease that have persistent tremor despite treatment with carbidopa/levodopa or dopamine agonists.

- Anticholinergic agents: There is little evidence to suggest that one anticholinergic agent is superior to another. Trihexyphenidyl is the most widely prescribed anticholinergic agent in the MTFs, with benztropine being reserved for use in the management of antipsychotic drug-induced Parkinsonism. The adverse effects of the anticholinergic medications are common and often limit their use, especially in the elderly population.
- Amantadine is an antiviral agent that has mild antiparkinsonian activity with its main advantage being a lower side effect profile than the anticholinergic agents. All three agents are available as generics and are inexpensive.

Since the goal of treatment for Parkinson's is control of symptoms, and no drug gives excellent relief by itself, the Council voted to add these three medications to the BCF.

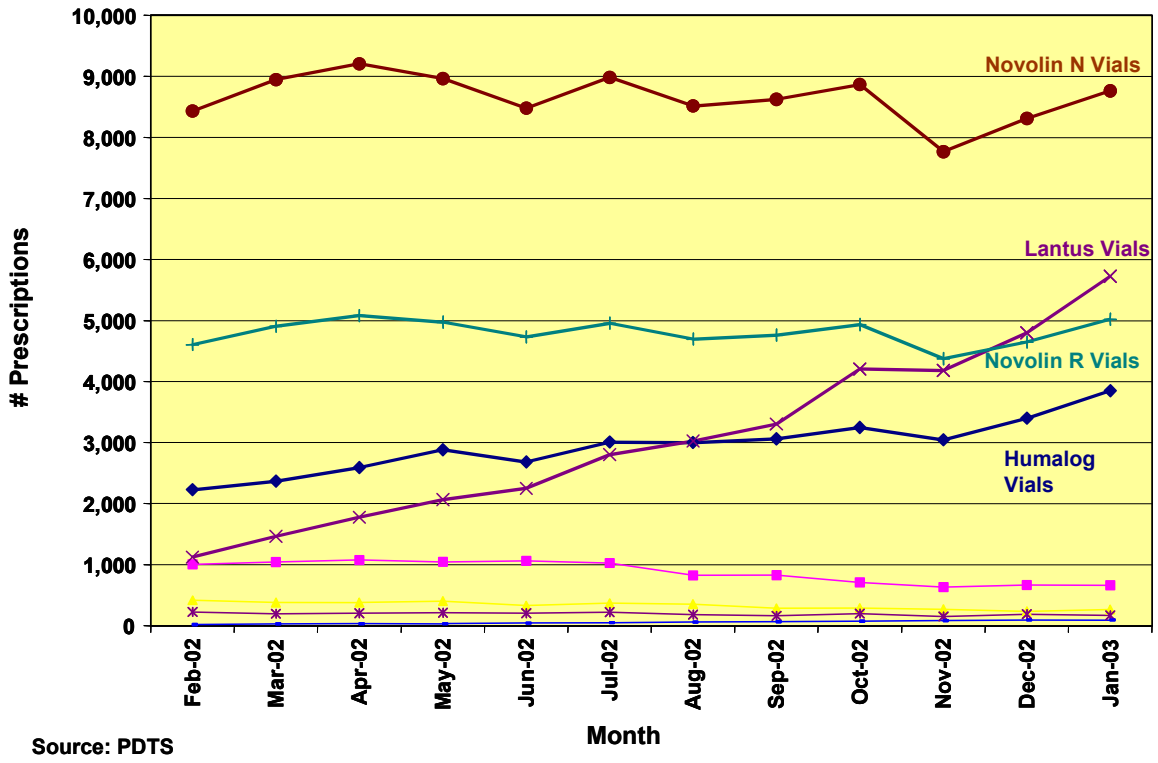
Dopamine agonists: A recent consensus opinion stated that dopamine agents are appropriate for the initial treatment of Parkinson's disease. Controlled trials have shown that bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapax), and ropinirole (Requip) are all effective in patients with advanced Parkinson's disease complicated by motor fluctuations and dyskinesias. Dopamine agonists, however, are ineffective in patients who have shown no therapeutic response to carbidopa/levodopa. Side effects caused by dopamine agonists are similar to those of levodopa and patients who are intolerant of one agonist may tolerate another. The Council requested the PEC conduct a drug class review to determine which, if any, dopamine agonists, to add to the BCF.

C. *Insulin Pens* – CAPT Torkildson discussed the need to consider the addition of insulin pens and/or cartridges to the BCF. This question had been raised following the addition of insulin glargine (Lantus) to the BCF in August 2002. A perception had developed that this would result in an increased utilization of these insulin delivery systems, especially for the pre-prandial administration of short-acting and ultra-short-acting insulins. A joint contract was awarded to Novo Nordisk Pharmaceuticals, Inc. in 1999 to provide the DoD and VA with human regular, NPH, lente, and NPH/regular 70/30 mix insulin products. However, this contract included only the 10 ml vial package size of these products. Since the cost per unit of insulin delivered is much higher for the pen and cartridge delivery systems

compared to vials, and these delivery systems are not included in the current insulin contract, the PEC felt it would be prudent to look at this issue in greater detail.

CAPT Torkildson presented current data regarding insulin utilization within the direct care system (see Figure 1). Two of the top four insulin products by prescription volume (Novolin N and Novolin R) are currently under contract, while the other two products (Lantus and Humalog) are not. The other two contracted insulin products, Novolin L and Novolin 70/30, have no appreciable utilization at MTFs. A similar usage pattern exists in the mail order program.

Figure 1: MTF Prescription Volume for Most Commonly Prescribed Insulin Products

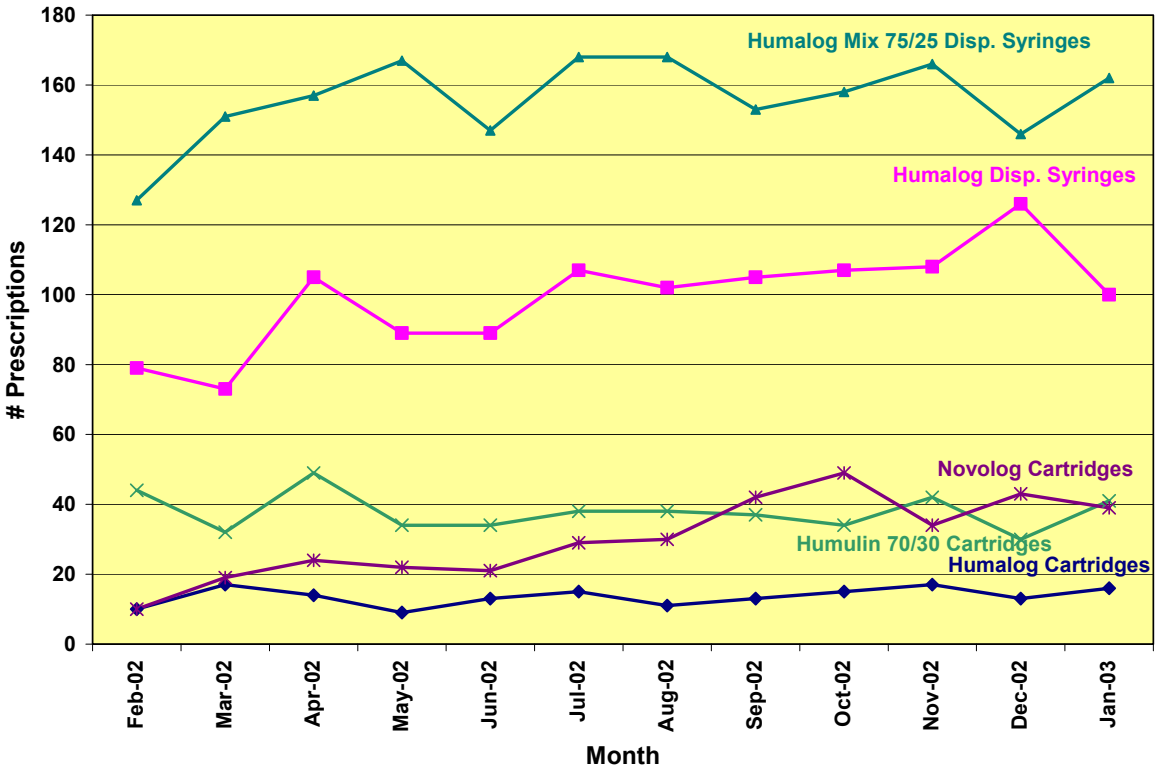


Source: PDTS

The data on utilization of insulin pens and cartridges within the direct care system is presented in Figure 2. Overall, insulin pens and cartridges currently represent a very small fraction of insulin product utilization. For the period 1 March 2002-28 Feb 2003, prescriptions for insulin pens and cartridges represented only 6% of the total number of insulin prescriptions filled in MTFs and the mail order program. However, as can be seen in Figure 2, the number of prescriptions for pen and cartridge delivery systems for ultra-short-acting insulin preparations (Humalog and Novolog) grew by about 50% over this period. In contrast, the prescription volume for other pen and cartridge insulin delivery products remained relatively flat. However, MTF expenditures for insulin pens and cartridges have increased

more rapidly. For example, MTFs spent $15,000 for Humalog pens in January 2003 compared to $5,000 in February 2002.

Figure 2: MTF Prescription Volume for Selected Insulin Disposable Syringe and Cartridge Products



A brief review of the clinical data highlighted the following information: While there are data to support the superiority of the ultra-short-acting insulin products (insulin lispro and insulin aspart) compared to regular insulin in terms of glycemic control, HbA1c levels, and frequency of hypoglycemia; there are currently no data that suggest that one ultra-short-acting insulin product is superior to the other. No data have been published since the award of the current insulin contract to suggest that any significant clinical differences exist between the products that were competed at that time, and no additional manufacturers of the products that are currently under contract have been identified.

From this information, the PEC came to the following conclusions:

- There is substantial and growing use of ultra-short-acting insulin products, primarily Humalog, at MTFs.
- There is almost no utilization of two of the four contracted insulin products, Lente and 70/30.
- There is currently little use of insulin pen devices.

- The monthly MTF expenditures for ultra-short-acting insulin pen devices has more than tripled over the past 12 months, from $6,000 to $20,000/month overall.

The PEC made the following recommendations to the Council:

- The DoD and VA should not exercise the final option year of insulin contract, which would begin on 1 November 2003
- The DoD and VA should instead begin development of a solicitation for a new insulin contract that covers different products than the current contract.
  - Lente insulin and the 70/30 product should not be included in the solicitation
  - The ultra-short-acting products (insulin lispro and insulin aspart) should be included in the solicitation
  - The pen/cartridge delivery system for the ultra-short-acting products only should be included in the solicitation

The Council voted unanimously to accept the PEC's recommendation and forward the above conclusions and recommendations for consideration by the Contracting Officer.

10. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Atypical antipsychotics* – The PEC is working on a review of the atypical antipsychotics. After the review is completed, the PEC will estimate the relative cost-effectiveness of the atypical antipsychotics and recommend how many of these agents should be added to the BCF.

B. *Ethinyl estradiol 20 mcg / Norelgestromin 150 mcg transdermal system (Ortho Evra)*

A MTF provider requested the addition of Ortho Evra to the BCF due to its unique administration route (topical) and potential for increased compliance.

Efficacy: A head-to-head that trial that compared 812 patients on Ortho Evra to 605 patients on Triphasil (30/40 mcg ethinyl estradiol with 50/75/125 mcg levonorgestrel) found that:

- The mean proportion of each participant's cycles that demonstrated perfect compliance was higher with Ortho Evra than with Triphasil (88.2% vs 77.7%, $p<0.0001$). [Note: Back-up contraception must be used if a patient exceeds a 7-day patch-free interval between Ortho Evra patches.]
- Despite better compliance with Ortho Evra, there was not a statistically significant difference in pregnancies: 5 with Ortho Evra vs 7 with Triphasil; $p=0.57$.

Safety/Tolerability: A higher percentage of patients on Ortho Evra discontinued the study due to adverse events than patients on Triphasil:

- Nausea: 1.8% with Ortho Evra vs 0.8% with Triphasil (p=0.12)
- Headache: 1.5% with Ortho Evra vs 0.3% with Triphasil (p=0.03)
- Dysmenorrhea: 1.5% with Ortho Evra vs 0.2% with Triphasil (p=0.01)
- Breast discomfort 1% with Ortho Evra vs 0.2% with Triphasil (p = 0.09)
- Application site reactions: 2.6% with Ortho Evra—not applicable for Triphasil

Other factors: A pooled analysis of clinical trial data (N=3319, 16,673 cycles) showed that 4.6% of Ortho Evra patches had to be replaced due to complete or partial detachment.

Price and usage: Ortho Evra costs $15.06/cycle, compared to $0.21-$8.00/cycle for oral contraceptives that are on the BCF. Ortho TriCyclen (which is not on the BCF) costs $15.21 per cycle. Ortho TriCyclen is the most commonly used contraceptive in the Military Health System (approximately 32,000 Rxs/month in all 3 points of service), compared to approximately 40,000 Rxs/month for all the oral contraceptives on the BCF combined. As of Jan 03, Ortho Evra had exceeded 10,000 Rxs/month.

The Council concluded that Ortho Evra does not offer any advantages in efficacy or safety/tolerability that justify its higher price compared to oral contraceptives already on the BCF. The Council voted unanimously not to add Ortho-Evra to the BCF.

C. *Topical Immunomodulators (TIMS)*

The PEC is still exploring procurement options for topical immunomodulators, so the Council took no action on these agents.

11. MTF REQUESTS FOR BCF CHANGES

A. *Request to add metoprolol extended release tablets (Toprol XL) to the BCF–* A MTF provider requested the addition of metoprolol succinate extended release tablets (metoprolol XL) to the BCF for congestive heart failure (CHF). The requestor's rationale was that "metoprolol XL is indicated for CHF and is not equivalent to the metoprolol tartrate immediate release preparation (metoprolol IR); additionally the XL formulation provides more dose flexibility by providing low doses to the patient and is the standard of care for CHF patients." No supporting literature was submitted along with the request.

Efficacy: Metoprolol XL is labeled for treating New York Heart Association (NYHA) functional class II/III CHF. A placebo-controlled trial conducted with metoprolol XL (MERIT-HF; Lancet 1999) in approximately 4000 subjects reported that 7.2% of patients receiving the drug died, compared with 11% in the placebo group (34% risk reduction, p<0.00009).

Metoprolol IR lacks an FDA-approved indication for CHF. A placebo-controlled trial conducted with metoprolol IR in approximately 400 patients with dilated idiopathic cardiomyopathy (MDC trial; Lancet 1993) found that 13% of patients

receiving the drug died, compared with 20% in the placebo group. The mortality rate of 13% is within range of the mortality rate seen in other beta blocker trials (7%-16%). Due to the small sample size, the survival benefit did not reach statistical significance ($p<0.058$). However, the risk reduction of 34% achieved with the metoprolol IR is similar to the risk reductions reported in other trials of similar design conducted with the beta blockers bisoprolol, carvedilol, and metoprolol XL.

The metoprolol IR study measured other parameters that showed significant benefits, including a reduced need for cardiac transplantation and improvements in left ventricular ejection fraction and exercise capacity. A head to head mortality study of metoprolol IR in comparison with carvedilol (COMET study) is currently underway in Europe, with results expected in summer 2003.

Safety/Tolerability: The XL formulation produces more consistent blood levels than the IR formulation. More consistent blood levels would theoretically produce more consistent beta-1 receptor blockade and cause fewer adverse events. However, head-to-head trials comparing metoprolol XL and metoprolol IR in small numbers of patients show no difference in safety and tolerability between the two formulations.

Other factors: Metoprolol IR is formulated in tablet strengths required for treating hypertensive patients (50 and 100 mg scored tablets), and is not available in the low doses required for initiating therapy in CHF patients (12.5 –25 mg). Metoprolol IR requires twice daily dosing. Metoprolol XL offers an advantage over metoprolol IR in that it is available in 25 mg scored tablets and is dosed once daily.

An analysis of PDTS prescription data showed that metoprolol XL is responsible for the 2nd highest number of beta blocker prescriptions in the NMOP and Retail Network, second only to atenolol. In the MTF setting, atenolol generates the most beta blocker prescriptions, followed by metoprolol IR, then metoprolol XL.

The Council voted unanimously not to add metoprolol XL to the BCF. Despite the lack of an FDA-approved indication, DoD providers use metoprolol IR for CHF. Although metoprolol XL offers the convenience of once daily administration and dosing flexibility, the absence of a significant difference in efficacy, safety or tolerability compared to metoprolol IR does not justify the higher expense for metoprolol XL ($9.90-$14.70 /month for metoprolol XL vs $0.90-$2.42/month for metoprolol IR). In the absence of a mechanism for MTFs to target the usage of metoprolol XL to patients with CHF, the addition of metoprolol XL to the BCF would likely result in increased use of metoprolol XL for hypertension in lieu of using other less-expensive beta blockers. The Council requested re-evaluation of the use of beta blockers for CHF upon completion of the COMET study.

B. *Request to add chlorthalidone 25 and 50 mg tablets to the BCF–* A MTF provider requested the addition of chlorthalidone, a generic thiazide diuretic, to the BCF in light of the recently completed landmark study (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALLHAT; JAMA 2002). This study showed that the thiazide diuretic chlorthalidone was equally efficacious to a

calcium channel blocker (amlodipine) and an ACE inhibitor (lisinopril) in reducing blood pressure in hypertensive patients, at a much lower cost than the other agents. Efficacy of chlorthalidone was also proven in the Systolic Hypertension in the Elderly Program (SHEP; JAMA 1991), which showed a reduced incidence of stroke and major cardiovascular events in the diuretic arm.

Chlorthalidone has historically has been used more commonly in Europe than the US. Chlorthalidone may have a higher incidence of hypokalemia than hydrochlorothiazide (HCTZ), however, all patients receiving thiazide diuretics require electrolyte monitoring. The incidence of hypokalemia (serum potassium < 3.5 mEq/L) in patients receiving chlorthalidone in both the ALLHAT and SHEP trials was <10% (8.5% and 7.2%, respectively).

Although current DoD utilization of chlorthalidone is low (10,000 chlorthalidone Rxs in all 3 venues, vs 1 million Rxs for HCTZ), the extensive publicity of the results of ALLHAT may cause usage to increase. HCTZ and chlorthalidone are both very inexpensive, with tablet costs as low as $0.01/tablet. Although the current BCF thiazide diuretic HCTZ meets the needs of the majority of DoD patients, practitioners of evidence-based medicine may want to use chlorthalidone, and its availability should be ensured at MTF pharmacies. Providers should be encouraged to take advantage of a low cost drug with excellent evidence of benefit in the treatment of hypertension. The Council voted unanimously to add chlorthalidone to the BCF.

12. ADJOURNMENT

The meeting adjourned at 1530 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Tuesday, 6 May 2003. All agenda items should be submitted to the co-chairs no later than 18 April 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **21 NOVEMBER 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 21 November 2002, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC (via VTC)	Air Force
COL Bill Sykora, MC	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Kathy Tortorice (Representing Dick Rooney)	Department of Veterans Affairs
Dr. Trevor Rabie	Uniformed Services Family Health Plan

VOTING MEMBERS ABSENT

Physician	Army

OTHERS PRESENT

LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board
Howard Altschwager	Deputy General Counsel, TMA
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
LtCol Dave Bennett, USAF, BSC (via VTC)	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
Maj Barb Roach, USAF, MC (via VTC)	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke (via VTC)	DoD Pharmacoeconomic Center
Eugene Moore (via VTC)	DoD Pharmacoeconomic Center
Angela Allerman (via VTC)	DoD Pharmacoeconomic Center
LT Chad McKenzie (via VTC)	DoD Pharmacoeconomic Center, Idaho State PharmD Internship
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
MAJ John Howe, MS	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Vincent Valinotti	Defense Supply Center Philadelphia
Mark Petruzzi	Medco Health
Elizabeth Scaturro	Medco Health
Victor Diaz, MD, MPH	Humana
William Hudson	Humana
Gene Lakey	TriWest
Ray Nan Berry	Health Net Federal Services
Lisa LeGette	DoD Tricare Information Center
LTC Emery Spaar	U.S. Army Officer resident at AMCP

3. **REVIEW MINUTES OF LAST MEETING**– The minutes from the last meeting were accepted as written.

4. **INTERIM/ ADMINISTRATIVE DECISIONS** –

A. *Membership*: Currently the DoD P&T Committee has 13 voting members. All other members are listed as other attendees. COL Remund will send out a copy of the existing charter to all members and recommendations for changes to the charter regarding membership should be sent to the chairs prior to the March meeting. The Council will decide at that time whether changes need to be made to the charter.

B. *Venlafaxine extended release capsules (Effexor XR) Blanket Purchase Agreement (BPA):* At the August 2002 meeting, the Council voted to add venlafaxine extended release 37.5, 75, and 150 mg capsules to the BCF, contingent on the signing of a BPA between Wyeth-Ayerst and DSCP. The BPA was recently signed, so Effexor XR is now on the BCF and facilities are required to include it on their formularies.

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- Howard Altschwager, TMA Deputy General Counsel, briefed the Committee on the status of the UF proposed rule. The TMA Pharmacy Program Office is currently in the process of formulating responses to comments submitted by the public.

6. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 13 new drugs or formulations (see Appendix A). The PEC also presented brief information on six additional new drugs or formulations not requiring a complete review by the Committee. The Committee agreed that no further review was required (see Appendix B for comments).

7. **NMOP AND RETAIL NETWORK ISSUES**

A. Review of the NMOP and retail network quantity limits for antiemetics – A review of the quantity limits established for oral 5-HT3 receptor agonists, used for the treatment of chemotherapy-induced nausea and vomiting, was initiated based on an inquiry received from a customer service representative at TMA West. A complaint was filed with this individual by a retired beneficiary, who stated that the quantity limit that currently exists was insufficient to meet the clinical needs of his wife, who was receiving treatment for cancer. CAPT Torkildson (PEC) performed the analysis and reported to the Committee.

There currently are three 5-HT3 receptor antagonists available in the U.S. for prophylaxis or treatment of chemotherapy-induced nausea or emesis: ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet). The P&T Committee established the following quantity limits for these products at their August 1999 meeting. These quantity limits apply both to the NMOP and the retail network:

Table 1: Quantity Limits for 5-HT3 Receptor Antagonists

Drug	30-day quantity limit	90-day quantity limit
Ondansetron tablets and orally disintegrating tablets	15	45
Granisetron tablets	8	24
Dolasetron tablets	5	15

In each case the quantity limit was established based on the drug's use for the FDA-approved indication: the prevention or treatment of chemotherapy induced nausea or vomiting. The first step of the analysis was to determine if additional FDA-approved indications had been added for one or more of these drugs that would materially change the number of tablets needed during a 30- or 90-day period. Since the quantity limits were initially established, the FDA has approved both ondansetron and granisetron for use in the prevention or treatment of nausea and vomiting associated with radiation therapy. Additionally, ondansetron and dolasetron were approved for treatment of postoperative nausea and vomiting. While the latter indication requires no modification in the quantity limit, the former could be associated with the use of a substantially greater number of tablets than specified by the current quantity limits. Based on the doses recommended for prevention or treatment of radiation-induced nausea and vomiting,

as many as 80 tablets of ondansetron or 40 tablets of granisetron could be required in a 30-day period, well above the current 30-day quantity limits for both products.

The second step of the analysis involved determining the actual number of tablets dispensed per prescription from each point of service and comparing these figures to the established quantity limits. In FY02, 29,645 oral 5-HT3 tablet prescriptions were filled in the MHS. Of these, 53% were filled at MTFs, 45% at retail network pharmacies, and 2% at the NMOP. Table 1 provides information regarding the number and percentage of prescriptions filled in each venue that exceed the currently established 30-day and 90-day quantity limits. No standard quantity limits exist at the MTFs; these figures are provided solely for comparison. It is notable that 13%-18% of prescriptions in the retail network exceed the established 30-day quantity limits. The representatives from each of the MCSC pharmacy benefit managers indicated that this was done only after a review was performed to ensure clinical appropriateness. A small number of prescriptions filled in the NMOP exceeded the 90-day quantity limit; Maj Bellemin indicated that this occurred only after a similar review process had taken been performed by him.

Table 2: Number (percentage) of Prescriptions Filled in FY 02 that Exceed Current NMOP and Retail Quantity Limits

		Point of Service		
Drug	**Qty Limit**	**MTF**	**Retail**	**NMOP**
Ondansetron 4 mg	> 15	1708 (52.2)	404 (13.2)	N/A
	> 45	427 (13)	63 (2.1)	1 (1.3)
Ondansetron 8 mg	>15	2897 (32.1)	812 (10.2)	N/A
	> 45	647 (7.2)	159 (2.0)	8 (3.1)
Granisetron 1 mg	> 8	468 (14.4)	196 (18.3)	N/A
	> 24	101 (3.1)	43 (4)	2 (4.1)
Dolasetron 50 mg	> 5	1 (100)	1 (5.6)	N/A
	> 15	1 (100)	0 (0)	0 (0)
Dolasetron 100 mg	> 5	37 (19.3)	177 (13.2)	N/A
	> 15	13 (6.8)	37 (2.8)	3 (5.6)

The conclusion reached by the PEC was that the current quantity limits are not sufficient to meet the clinical needs of patients undergoing radiation therapy. However, it does not appear that this creates a significant problem for patients. This is most likely due to two factors: 1) the low number of patients requiring treatment with antiemetics during their radiation therapy. Studies have suggested that only patients receiving higher dose abdominal radiation and some patients receiving radiation therapy to the head and neck will require antiemetic therapy. 2) a fair and effective review process for approval of prescriptions that exceed the established quantity limits. This is supported by the fact that only one complaint has been forwarded to the PEC in the three years since the quantity limits were established. Given the growing number of 5-HT3 receptor antagonist prescriptions being written for off-label indications such as hyperemesis gravidarum, the committee felt it would not be prudent to increase the quantity limits above the current levels, as these prescriptions should all be reviewed for clinical appropriateness. The PEC will monitor the situation and report back if the need arises.

8. **CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS** – Gamma hydroxy butyrate solution (Xyrem) has been approved by the FDA with distribution limited to a single pharmacy, Express Scripts' Specialty Distribution Services. Since Express Script's Specialty Distribution Services may not be a member of each MCSC network, patients will likely have to file out-of-network claims to get reimbursed for this drug. The MCSC Pharmacy Directors will look into enrolling Express Scripts into their networks so only a copay will be required.
9. **ADJOURNMENT –** The meeting adjourned at 1130 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Thursday, 6 March 2003. All agenda items should be submitted to the co-chairs no later than 14 February 2003.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Amoxicillin clavulanate extended release tablets (Augmentin XR; GSK)	2 Oct 02: Treatment of community acquired pneumonia (CAP) or acute bacterial sinusitis caused by beta-lactamase-producing bacteria or *Strep. pneumoniae* with reduced susceptibility to penicillin (e.g., penicillin MICs = 2 mcg/ml). Not indicated for treating infections due to *S. pneumoniae* with penicillin MIC [≥] 4 mcg/ml, due to only limited data. This formulation has 62.5 mg of clavulanate, instead of 125 mg found in other Augmentin preparations. The dose cannot be duplicated with existing Augmentin preparations. Augmentin XR still requires twice daily dosing; the controlled release mechanism appears to provide higher sustained blood levels of amoxicillin.	Added to the NMOP Formulary	**Quantity Limits** General Rule applies **Prior Authorization:** None	Not added to the BCF The BCF listing for amoxicillin/ clavulanate acid oral was clarified to exclude Augmentin XR **Similar BCF agents:** Amoxicillin/ clavulanate is listed on the BCF. The listing includes the pediatric suspension Augmentin ES-600. A generic version of Augmentin is now available.
Tazarotene 0.1% topical cream (Avage; Allergan)	2-Oct 02: Tazarotene is a retinoid prodrug. As Avage, it is indicated for palliation of facial fine wrinkling, hyper- and hypo-pigmentation, and benign facial lentigines in patients using skin care and sunlight avoidance programs. The same active ingredient (0.1% tazarotene) is marketed in a gel formulation under the trade name Tazorac, with indications for the treatment of psoriasis and acne vulgaris.	The Avage brand of tazarotene was specifically excluded from the NMOP Formulary, since its use is limited to cosmetic applications; other drugs intended solely for cosmetic use as a result of the aging process have been determined to be excluded from coverage by TRICARE rule. Tazorac usage will be monitored for any changes in age distribution.	**Quantity Limits** General rule applies. **Prior Authorization** None	Not added to the BCF. **Similar BCF agents:** Tretinoin 0.05% and 0.025% topical cream is listed on the BCF; the listing excludes Renova, a product that is only indicated for wrinkles.
Clindamycin 1% / benzoyl peroxide 5% topical gel (Duac; Steifel Labs)	26 Aug 02: Topical treatment of inflammatory acne vulgaris. This is the second clindamycin 1% / benzoyl peroxide 5% combination product to become available. The other product (BenzaClin; Aventis) is available in 25 and 50-gram jars that require reconstitution prior to dispensing. The Duac product does not require reconstitution; it is available in a 45-gram tube.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Clindamycin 1% solution

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Glipizide / metformin tablets (Metaglip; BMS)	21 Oct 02: Initial therapy in type 2 diabetics who are not achieving adequate glycemic control with diet and exercise alone. Also approved for second-line therapy in patients with type 2 diabetes who are not achieving adequate glycemic control with diet, exercise, and initial treatment with metformin or a sulfonylurea.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Metformin is listed on the BCF; a mandatory source contract is in effect. Glipizide immediate release is also listed on the BCF
Rosiglitazone / metformin tablets (Avandamet; GSK)	10 Oct 02: Use as an adjunct to diet and exercise in type 2 diabetics who are already receiving rosiglitazone and metformin as separate tablets, or who are not adequately controlled with metformin alone (second line therapy). Avandamet is not labeled for use as initial therapy in type 2 diabetics.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Metformin is listed on the BCF; a mandatory source contract is in effect. The DoD P&T committee has recommended addition of a TZD to the BCF; a contracting solicitation is in progress.
Dutasteride tablets (Avodart; GSK)	9 Oct 02: Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to include: Symptom reduction of BPH Reduction of the risk of urinary retention associated with BPH Reduction of the risk of BPH-related surgery	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None. The alpha-blockers terazosin and prazosin are BCF items
Ethinyl estradiol 25 mcg / norgestimate tablets (Ortho Tri-Cyclen Lo; Ortho McNeil)	22 Aug 02. Prevention of pregnancy. Oral tri-phasic contraceptive containing 25 mcg of ethinyl estradiol, and three different doses of norgestimate, a low androgenic-potential progestin. Ortho Tri-Cyclin Lo is not indicated for acne.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: No low estrogen triphasic OCPs are listed on the BCF. A low-dose monophasic preparation (20 mcg ethinyl estradiol / 1 mg norethindrone / 75 mg ferrous fumarate (Loestrin FE or its generic equivalent) was added to the BCF at this meeting.

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Alosetron tablets (Lotronex; GSK)	7 Jun 02; treatment of severe diarrhea-predominant irritable bowel syndrome in women who have failed to respond to conventional therapy. Alosetron is not expected to be available until Dec 2002. A controlled distribution program is in place that requires physician self-certification and stickers to be placed on all prescriptions. More information is available on the FDA web site at http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm. Alosetron was originally pulled off the market in Jun 2000 due to cases of GI toxicity (ischemic colitis ad constipation resulting in 2 deaths). The new indication is narrower than the original labeling, and the dosage is now 1 mg qd instead of 1 mg bid.	Added to the NMOP Formulary. The controlled distribution program requirements can be met through the NMOP, however faxed prescriptions cannot be accepted.	**Quantity Limits** General rule applies; however, the controlled distribution program will necessitate dispensing in pre-packaged quantities. The NMOP will fill Rxs with the amount of tablets that is as close as possible to the original Rx. **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** None
Tegaserod tablets (Zelnorm; Novartis)	6 Aug 02: short-term treatment of constipation-predominant irritable bowel syndrome.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None
Adefovir tablets (Hepsera; Gilead)	20 Sep 02 (priority review): treatment of chronic hepatitis B in adults with evidence of active viral replication and either elevations in ALT or AST, or histologically active disease. Labeling has evidence of efficacy for lamivudine-resistant hepatitis B.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: None
PEG interferon alfa-2a injection (Pegasys; Roche)	16 Oct 02: treatment of adults with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alfa	Added to the NMOP Covered Injectables List	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF. Re-examine potential BCF addition in 3-6 months. **Similar BCF agents:** None
Comments regarding pegylated interferon alfa products for hepatitis C: PEG interferon alfa-2a (Pegasys) is not associated with a patient enrollment program; supplies are expected to be sufficient to meet demand. Schering's peg interferon alfa-2b product (PEG-Intron) previously had a patient enrollment program, but it was recently discontinued. The P&T Committee decided to readdress the potential BCF addition of a pegylated interferon alfa product for hepatitis C in 3-6 months.				

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Ezetimibe tablets (Zetia; Merck)	25 Oct 02: Treatment of: Primary Hypercholesterolemia: Monotherapy – as an adjunct to diet to reduce TC, LDL-C, and Apo B Combination therapy – when administered with a statin as an adjunct to diet to reduce TC, LDL-C, and Apo B Homozygous familial hypercholesterolemia: when used in combination with atorvastatin or simvastatin Homozygous sitosterolemia: as an adjunct to diet	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF. The P&T Committee voted to reconsider BCF addition of ezetimibe in 6 months **Similar BCF agents**: None
Guaifenesin extended release tablets (Mucinex; Adams Labs)	As of 12 Jul 2002, Mucinex (Adams Labs) became the first single ingredient guaifenesin extended release product to be 1) approved as safe and effective under a New Drug Application (NDA) and 2) to be approved as an over-the-counter (OTC) product. As a consequence of approval, the FDA has sent warning letters to manufacturers of guaifenesin extended release products explaining that currently marketed single ingredient guaifenesin extended release products without an approved application are considered misbranded and in violation of section 505(a) of the Food, Drug, and Cosmetic Act (FDCA). In addition, provisions of the Durham-Humphrey amendment (products cannot be marketed as both Rx and OTC products) effectively mean all single ingredient extended release will be OTC products. At least one affected manufacturer is known to be petitioning this action, but it is not known if any single ingredient guaifenesin extended release product other than Mucinex will continue to be available in the near future.	Since single ingredient guaifenesin extended release products are now OTC products, they will no longer be available from the NMOP and will not be included on the NMOP Formulary. Prescription extended release guaifenesin products will be dispensed by the NMOP as long as current supplies permit.	**Quantity Limits** N/A **Prior Authorization** None	The DoD P&T Executive Council removed the BCF listing for guaifenesin 600 mg extended release. MTFs may decide whether to retain the product on their formularies or not. See minutes of the DoD P&T Executive Council meeting for more information.

APPENDIX B: NEWLY APPROVED DRUGS NOT REQUIRING FULL REVIEW BY THE P&T COMMITTEE

Generic (Trade name; manufacturer)	**Indication**	**Comments**
Oxaliplatin injection (Eloxatin; Sanofi)	Treatment of metastatic colon/rectal CA in combination with 5-FU and leucovorin.	Not considered for the NMOP Formulary since the injection is not designed for self-administration. Not considered for the BCF due to the specialized nature of the indication.
Rasburicase injection (Elitek; Sanofi)	Orphan drug for the management of uric acid levels in pediatric patients receiving chemotherapy.	Not considered for the NMOP Formulary since the injection is not designed for self-administration. Not considered for the BCF due to the specialized nature of the indication.
Urokinase injection (Abbokinase; Abbott)	Treatment of thrombolysis of acute PE. Indication for catheter clearance is underway. Re-introduced 10 Oct 02, following market withdrawal in 1999 due to manufacturing problems.	Not considered for the NMOP Formulary since the injection is not designed for self-administration and because of the emergent nature of the indication. Not considered for the BCF due to the specialized nature of the indication and the emergent nature of the indication.
Buprenorphine / naloxone; buprenorphine tablets (Suboxone; Subutex; Schering Plough)	Treatment of opioid dependence. Patients can be treated in MD offices outside of methadone maintenance programs. Controlled distribution program is in effect.	Not considered for the NMOP Formulary because a legal interpretation is needed to determine if treatment of opioid dependence outside of a methadone maintenance program is a covered Tricare benefit. It is not known if requirements of the controlled distribution program could be meet in the NMOP. Not considered for the BCF due to the specialized nature of the indication.
Sodium oxybate (gamma hydroxy butyrate) solution (Xyrem; Orphan Medical)	Treatment of cataplexy related to narcolepsy	Not considered for the NMOP Formulary because availability from the NMOP is not feasible; the restricted distribution program for this product is limited to a single pharmacy (see Paragraph 8 in these minutes). Not considered for the BCF due to the specialized nature of the indication.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. BCF CHANGES

A. Additions to the BCF

1) Tolterodine extended release capsules (Detrol LA)
2) Timolol maleate, solution, gel-forming 0.25%, 0.5% (Timoptic XE; Merck brand only - mandatory source contract)
3) Norethindrone/EE/ferrous fumarate 1/0.02 mg (Loestrin FE or its generic equivalent [Microgestin FE])
4) Niacin extended release tablets (Niaspan)
5) Venlafaxine extended release capsules (Effexor XR)

B. Deletions from the BCF

1) Niacin immediate release oral
2) Guaifenesin 600 mg extended (sustained) release tablets

C. Changes and clarifications to the BCF - None

D. Exclusions from the BCF

1) Paroxetine controlled release (Paxil CR) was excluded from the BCF listing for paroxetine
2) Amoxicillin/clavulanate extended release tablets (Augmentin XR) were excluded from the BCF listing for augmentin/clavulanate acid oral

2. NMOP FORMULARY CHANGES

A. Additions to the NMOP Formulary

1) Augmentin/clavulanate acid extended release tablets (Augmentin XR; GSK)
2) Clindamycin 1%/benzoyl peroxide 5% topical gel (Duac; Steifel Labs)
3) Glipizide / metformin tablets (Metaglip; BMS)
4) Rosiglitazone/metformin tablets (Avandamet; GSK)
5) Dutasteride tablets (Avodart; GSK)
6) Ethinyl estradiol 25 mcg/norgestimate (varying doses) tablets (Ortho Tri-Cyclen Lo; Ortho McNeil)
7) Alosetron tablets (Lotronex; GSK) – The controlled distribution program requirements can be met through the NMOP, however faxed prescriptions cannot be accepted.
8) Tegaserod tablets (Zelnorm; Novartis)
9) Adefovir tablets (Hepsera; Gilead)
10) PEG interferon alfa-2a injection (Pegasys; Roche) – added to the NMOP Covered Injectables List
11) Ezetimibe tablets (Zetia; Merck)

B. Exclusions from the NMOP Formulary

1) Avage brand of tazarotene 0.1% topical cream (Allergan) – specifically excluded from the NMOP Formulary, since its use is limited to cosmetic applications; other drugs intended solely for cosmetic use as a result of the aging process are not available from the NMOP.

C. Removed from the NMOP Formulary; no longer available from the NMOP

1) Single ingredient guaifenesin extended release tablets – approved as an OTC product 12 July 02

D. Clarifications to the NMOP Formulary - None

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK) -** None

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)** - None

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **20 November 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1515 hours on 20 November 2002 at the Uniformed Services University of the Health Sciences, Bethesda, Maryland.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC (via VTC)	Air Force
COL Bill Sykora, MC	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Kathy Tortorice (Representing Dick Rooney)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

Physician	Army

OTHERS PRESENT

COL Geoffrey W. Rake, MC	Medical Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
MAJ John Howe, BSC	Defense Supply Center Philadelphia
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Vincent Valinotti	Defense Supply Center Philadelphia
LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
COL Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC (via VTC)	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC (via VTC)	DoD Pharmacoeconomic Center
LT Chad McKenzie, MSC (via VTC)	DoD Pharmacoeconomic Center, Idaho State PharmD Internship
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke (via VTC)	DoD Pharmacoeconomic Center
Eugene Moore (via VTC)	DoD Pharmacoeconomic Center
Angela Allerman (via VTC)	DoD Pharmacoeconomic Center
CAPT Sandra Yerkes, MC	Deputy, Chief Medical Corps BUMED
LTC Emery Spaar, MS	U.S. Army Officer resident at AMCP
Michael Valentino	Department of Veterans Affairs, PBM

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. Membership: Currently the DoD P&T Executive Council has 12 voting members and the DoD P&T Committee has 13 voting members. All other members are listed as others present. COL Remund will send out a copy of the existing charter to all members and recommendations for changes to the charter regarding membership should be sent to the chairs prior to the March meeting. The Council will decide at that time whether changes need to be made to the charter.

B. Venlafaxine extended release capsules (Effexor XR) blanket purchase agreement (BPA): At the August 2002 meeting, the Council voted to add venlafaxine extended release 37.5, 75, and 150 mg capsules to the BCF, contingent on the signing of a BPA between Wyeth-Ayerst and Defense Supply Center Philadelphia (DSCP). The BPA was recently signed, so Effexor XR is now on the BCF and facilities are required to include it on their formularies.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

Contract awards, renewals, and terminations

- New joint DoD/VA contracts were awarded for albuterol inhaler and lisinopril (West-ward; bottles of 100 effective November 21, 2002 and bottles of 1000 effective March 2003).
- The following joint DoD/VA contracts were not awarded because the bid prices were higher than existing FSS prices: penicillin, amoxicillin, dicloxacillin, and cephalexin.
- The following joint DoD/VA contract is in various stages of solicitation: tretinoin cream.

6. PENDING PROCUREMENT INITIATIVES

A. Status of contracting initiatives

- The joint DoD/VA solicitation for a leutinizing hormone releasing hormone (LHRH) agonist has closed. An award is expected in January 03.
- A joint DoD/VA solicitation will not be issued for a nasal corticosteroid. A DoD/VA incentive agreement for fluticasone (Flonase) is being developed and will likely be finalized in December 02.
- A joint DoD/VA solicitation for a "triptan" has been issued and is scheduled to close in early December.
- A revision of the current incentive agreement for levofloxacin is being negotiated.
- A joint DoD/VA solicitation is being developed for an angiotensin receptor blocker (ARB) and is scheduled to be issued during the first quarter of CY 03.
- A joint DoD/VA solicitation for a "statin" is scheduled to be issued in late December 02.
- A joint DoD/VA solicitation for a thiazolidinedione is being developed. A projected issue date is not yet identified.
- The lisinopril contract has been awarded. Details are available at: http://www.dmmonline.com/pharm/indivdrugs.asp?id=83

B. Proposed BPA for tolterodine extended release capsules (Detrol LA) – In June 2001 the Council discussed the drugs used for treating overactive bladder (OAB) in response to several requests to add Detrol LA to the Basic Core Formulary (BCF). At that time the Council concluded that none of the drugs should be added to the BCF because none of them offered sufficient clinical benefit to justify their significantly higher cost compared to oxybutynin immediate release. Pharmacia is now offering a BPA that would reduce the price of Detrol LA if it were added to the BCF.

The Council considered the following information:

- A head-to-head study of Ditropan XL and Detrol LA found that Detrol LA was better tolerated (patients' perceptions reported on a visual analog scale) and slightly more effective (patients' perceptions reported on a 6-point Likert scale)
- An analysis of PDTS data from Jul 01 to Oct 02 showed that 58.4% of patients prescribed Detrol LA obtained at least one refill of their prescription, compared to only 36.7% for Detrol, 36.1% for Ditropan XL, and 30.7% for oxybutynin immediate release. The higher

refill rate for Detrol LA may indicate that patients tolerate it better than other agents and/or that patients perceive that it works better than the other agents.

- Dr. John Fischer, an Air Force urogynecologist, briefed the Council via VTC on his clinical experiences with patients and patient perceptions of benefit. Dr. Fischer recommended that the Council add Detrol LA to the BCF.
- Detrol LA usage has increased much more than other agents for OAB. Data from all outpatient pharmacy points of service in the MHS show that the number of patients getting prescriptions filled for Detrol LA more than tripled from 4,000 patients in Jul 01 to nearly 13,000 patients in Oct 02.

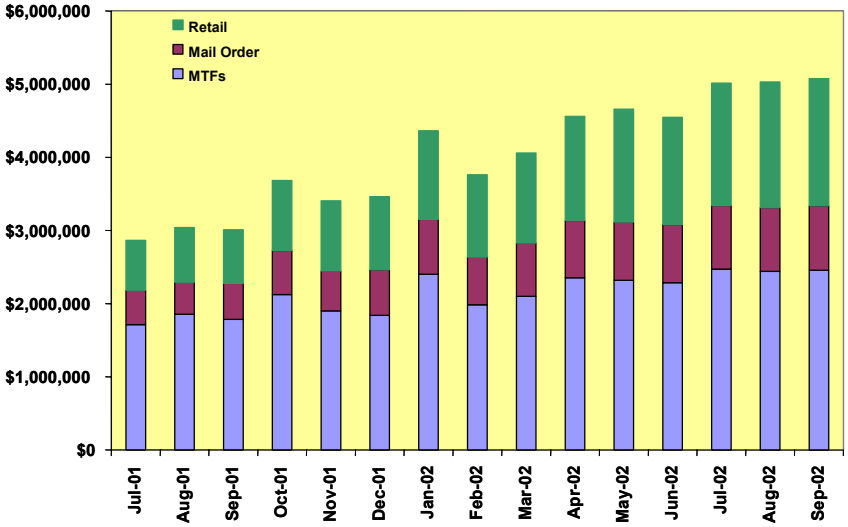
The Council voted to add Detrol LA to the BCF and advise DSCP to accept the proposed BPA.

7. **GENERIC CONTRACTS -** CDR (sel) Ted Briski informed the Council that some solicitations for joint DoD/VA generic contracts do not elicit competitive bids because the generic companies have trouble meeting the large demand from both agencies. He asked the Council whether the need for standardization was still a legitimate reason for pursuing these contracts. Council members stated that standardization is needed by both agencies, particularly to support the use of automation. The Council suggested the two agencies might be more successful by pursuing separate contracts to avoid overwhelming the production capabilities of the generic manufacturers. CDR (sel) Briski stated he would work with the Federal Pharmacy Executive Steering Committee (FPESC) sub-committee for contracting to find viable solutions to the problems encountered. The Council unanimously agreed on the motion to strive to achieve inter-agency standardization through whatever means are available.

8. **ARB Place In Therapy (PIT) Recommendation –** The Council discussed a draft of the Angiotensin II receptor blocker (ARB) place in therapy recommendations. The Council had requested guidelines for ARB use at the last meeting as part of their decision to pursue a procurement strategy to select one of these agents for BCF status, as these agents are significantly more expensive than ACE inhibitors, and their place in therapy is not yet clearly defined. The PIT recommendation is intended to aid practitioners in the appropriate use of the ARBs, and provides a summary of the literature for use in hypertension, congestive heart failure, and diabetic nephropathy. COL Downs expressed concern about the designation of ARBs as the initial agents of choice for diabetic nephropathy in Type 2 diabetes. Members also expressed concern about placement of pricing information at the beginning of the document. The Council asked the Pharmacoeconomic Center (PEC) to work with COL Downs to revise the document and report back at the next meeting.

9. **DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES**:

A. Bisphosphonates — Oral bisphosphonates are the most frequently prescribed drug therapy for the treatment of osteoporosis. Alendronate and risedronate are currently indicated for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease. Alendronate is also indicated for osteoporosis in men. Both bisphosphonates are available in daily or weekly dosing formulations. The weekly dosage forms account for the majority of DoD usage. The DoD now spends about $5 million a month on oral bisphosphonates across all outpatient pharmacy points of service. Bisphosphonates rank number 8 in Military Treatment Facility (MTF) overall drug expenditures.



MHS Bisphosphonate Monthly Expenditures

Source: PDTS & Prime Vendor Data

Therapeutic Interchangeability:

- *Efficacy* – There are no head-to-head trials that compare fracture rates for alendronate and risedronate. Tables 1-4 in Appendix A show 'funnel' diagrams of the relative risk of vertebral and non-vetebral fractures for each drug compared to placebo from a recently published meta-analysis. Table 5 in Appendix A shows the results of studies that compared each drug to placebo for hip fractures. In their responses to a PEC survey, 50 out of 57 DoD providers stated that they believe alendronate and risedronate have similar efficacy. The Council concluded that alendronate and risedronate have similar efficacy in reducing fractures.
- *Safety/Tolerability* – Oral bisphosphonates are well tolerated when taken according to manufacturers' recommendations. Clinical trials show adverse event rates that are not statistically different from placebo, but gastrointestinal disturbances (sometimes severe) can occur if patients do not follow dosing instructions. Two head-to-head trials examined the tolerability of alendronate and risedronate. The first head-to-head trial compared 28-day regimens of alendronate 40 mg and risedronate 30 mg. The study failed to find a statistically significant difference in endoscopically diagnosed ulceration or patient-reported GI toxicity. The second study evaluated 14-day regimen of alendronate 10 mg and risedronate 5mg. A significant difference in endoscopically diagnosed ulceration was found for gastric ulcers (13.2% for alendronate group and 4.1% for risedronate group), but not for esophageal or duodenal ulcers. No significant difference in patient-reported upper GI adverse events was seen between each group and no correlation was found between upper GI events and the presence or absence of gastric or esophageal ulcers. An accompanying editorial regarding this study stated, "the clinical relevance of small endoscopic ulceration observed is unclear." The editorial also stated, "it is controversial whether acute endoscopically diagnosed superficial mucosal injury (including gastric ulcers as small as 3mm in diameter) is at all related to subsequent development of serious clinical consequences..." The Council concluded that alendronate and risedronate are similar in regard to safety and tolerability.

Coverage of Clinical Needs: Although alendronate is the only bisphosphonate that has an FDA-approved indication to increase bone mass in men with osteoporosis, an analysis of DoD prescription data showed that the percent of total days of therapy dispensed to men were similar for both alendronate and risedronate. The difference in FDA-approved indications does not

appear to affect usage of the two drugs in clinical practice. The Council concluded that either agent would likely meet the clinical needs for more than 90% of the population requiring treatment.

Provider Acceptance:

- *New Starts*- The majority (48 - 7) of providers responding to a PEC survey were willing to use either agent equally. Some providers preferred alendronate because of its indication for osteoporosis in men and perception of greater efficacy in reducing hip fractures.
- *Patient Switches* – The majority (43 - 16) of providers were also willing to switch current patients to the selected agent if the switch could be done at a regularly scheduled visit rather than incurring an extra visit.

The Council voted unanimously to support any contracting/formulary strategy (to include a closed class contract with patient switches) designed to lower the cost of bisphosphonate drug therapy for DoD.

B. Glaucoma Agents — Primary open-angle glaucoma (POAG) is the most common type of glaucoma. POAG leads to progressive visual field loss followed by central field loss, usually but not always in the presence of elevated intraocular pressure (IOP). Lowering IOP remains the primary modality for therapy for POAG and appears to protect against further damage. The therapy for POAG often is characterized by poor compliance since POAG is entirely asymptomatic.

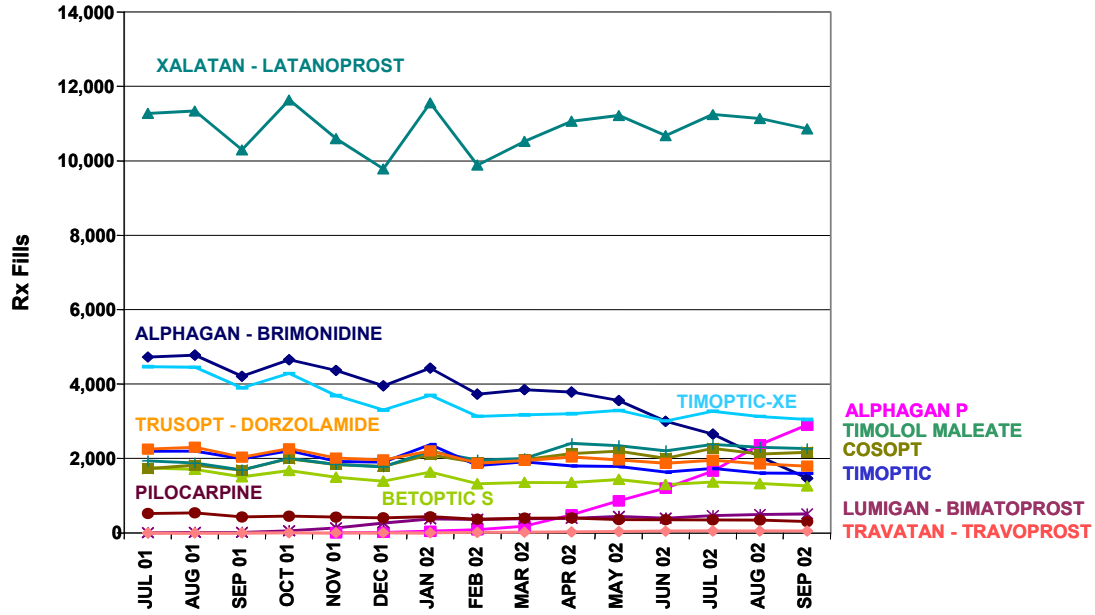
High utilization of latanoprost (Xalatan) and timolol maleate gel (Timoptic XE), which are not currently on the BCF, and new products for the treatment of glaucoma, triggered this class review. The PEC also received a request from the field to delete pilocarpine from the BCF due to low utilization.

Currently the BCF contains the following glaucoma medications:

- *Topical β-blocker* (timolol 0.25%, 0.5% ophth soln – Alcon Labs brand only- DoD mandatory source contract): This drug effectively lowers IOP by 27-35% and is considered initial drug therapy in primary open angle glaucoma (POAG) and ocular hypertension, except in patients with cardiac or pulmonary contraindications. Topical β-blockers have few ocular side effects, however major side effects are similar to those associated with systemic beta-blocker therapy (worsening of heart failure, bradycardia, heart block, and increased airway resistance). The current BCF listing does not include timolol maleate gel (Timoptic XE), which is applied once daily vs. the twice-daily ophthalmic solution.
- *Sympathomimetic agent* (brimonidine 0.15% ophth soln – Alphagan P): Efficacy studies report a decrease in IOP of 20-27%. These agents are indicated for both short-term treatment to prevent intraocular pressure (IOP) spikes after laser trabeculoplasty and for chronic treatment in patients with ocular hypertension or POAG. The Alphagan Purite 0.15% formulation has a 41% lower rate of ocular allergy than brimonidine 0.2% resulting in a reduced rate of discontinuation due to adverse events.
- *Miotic* (pilocarpine ophthalmic solution): Efficacy studies report a decrease in IOP of 20-30%. Pilocarpine's unique place in therapy is in the use for glaucoma emergencies such as acute angle closure glaucoma and glaucoma laser surgery.

MTF RX Fills for Anti-glaucoma Agents

(July 01-September 02)



Source: PDTS

The BCF does not contain medications in the following classes of glaucoma medications:

- *Carbonic anhydrase inhibitors (CAI):* Acetazolamide is the most commonly used oral CAI. These drugs effectively lower IOP by 20-40% with low ocular adverse effects, however their systemic adverse effects hamper their use in the management of glaucoma. These agents are contraindicated in patients with renal failure, hepatic insufficiency, lowered plasma potassium and sodium levels, and chronic obstructive pulmonary disease. Due to low utilization of these agents and their poor tolerability these agents were not considered for BCF inclusion.
- *Prostaglandins (latanoprost, bimatoprost, travoprost, unoprostone)*: These agents are indicated for the reduction of elevated IOP in patients with open angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

Despite their "second line" place in therapy, the prostaglandin class has been targeted for a procurement strategy due to increased utilization, increased cost, and potential for price competition due to the number of agents in the market basket. A significant price reduction might be achieved through a procurement initiative that places one or more prostaglandin on the BCF. The following analysis focuses on prostaglandins.

Prostaglandin Clinical Efficacy: Clinical trials have not demonstrated *a priori* that treating to predefined IOP targets preserves vision. Nor have there been clinical trials demonstrating that more aggressive IOP lowering targets result in preservation of vision. Limited observational data suggests that patients achieving lower IOP with combined surgical and medical treatment experience less visual field deterioration. Finally, there are no clinical trials comparing the amount of preservation of visual acuity afforded by the different topical ophthalmic drops. All

comparisons of efficacy rely on the surrogate marker of lowering IOP. A measurement error of 1-2 mmHg may be seen in IOP measurement.

Randomized controlled clinical trials demonstrated that bimatoprost, travoprost, and latanoprost given once daily produced equal or superior efficacy to twice-daily timolol. Appendix B shows the results of prostaglandin head-to-head comparison trials.

Prostaglandin Safety and Tolerability: Both bimatoprost and travoprost have shown to have statistically significant more cases of hyperemia and pruritis than latanoprost. Mean hyperemia scores in all treatment groups, however, were in the trace to mild hyperemia range. Local adverse effects seem to be unassociated with long-term effects or increased discontinuation of medications in the clinical trials. See table 1 for adverse events related to prostaglandin ophthalmic agents found in head-to-head comparison trials.

Table 1: Adverse events related to prostaglandin ophthalmics

Study	Adverse Event	Timolol 0.5%	Latanoprost 0.005%	Bimatoprost 0.03%	Travoprost 0.004%	Unoprostone 0.12%
Tin Aung 2001	Ocular irritation	N/A	12/37 (32%)	N/A	N/A	21/34 (62%)
	Iris pigment changes	N/A	0	N/A	N/A	0
	Eye redness	N/A	13/37 (35%)	N/A	N/A	6/34 (18%)
Netland 2001	Hyperemia*	14%	27.6%	N/A	49.5%	N/A
	Iris pigment changes*	0%	5.2%	N/A	3.1%	N/A
	Eyelash changes*	3.1%	25.8%	N/A	57.1%	N/A
Gandolfi 2001	Hyperemia*	N/A	14.2%	36.1%	N/A	N/A
	Iris pigment changes	N/A	Not reported	Not reported	N/A	N/A
	Eyelash changes*	N/A	4.4%	12.6%	N/A	N/A
DuBiner 2001	Hyperemia	N/A	3/21 (14%)	3/21 (14%)	N/A	N/A
	Iris pigment changes	N/A	Not reported	Not reported	N/A	N/A
	Eyelash changes	N/A	Not reported	Not reported	N/A	N/A

Tin Aung: One patient on latanoprost did not complete the study because of severe swelling of the eyelids.
Netland: No reported discontinuations in article due to adverse events
Gandolfi: Six bimatoprost patients discontinued due to adverse events: 4 due to ocular events, 2 due to systemic and ocular adverse events. Five latanoprost patients discontinued due to adverse events: 2 due to ocular events, 3 due to systemic and ocular adverse events.
DuBiner: One patient discontinued from the latanoprost group because of body aches and stomach cramps. Two patients discontinued from the bimatoprost group because of ocular symptoms (eyelid edema, conjunctival hyperemia, foreign body sensation) or nausea and ocular symptoms (eyelid edema, asthenopia, conjunctival hyperemia).

Therapeutic Interchangeability: Unoprostone is not considered therapeutically equivalent to latanoprost, bimatoprost or travoprost because of its lower efficacy (Appendix B, Table 1) and twice-daily dosage schedule. Latanoprost, bimatoprost, and travoprost have each been demonstrated to provide statistically significantly greater reductions in IOP than timolol. Head-to-head trials did not show statistically significant differences between latanoprost and travoprost 0.004% or between latanoprost and bimatoprost in lowering IOP. Post-hoc subgroup analysis of the data from the clinical trial by Netland et al. showed that travoprost lowered IOP more than latanoprost at specific time points among African American study subjects. However, the IOP differences in the travoprost vs. latanoprost group in African American patients during treatment may have resulted from preexisting differences in baseline IOPs, some of which were statistically significant. If the results were expressed as a change in IOP from baseline measurements, no significant difference in efficacy of the drugs in African American population exists. The effect of travoprost in the African American population requires further analysis and clarification.

Both bimatoprost and travoprost may have more hyperemia and pruritis than latanoprost, but less iris or eyelash pigment changes. Mean hyperemia scores in all treatment groups were in the trace and mild hyperemia score. Local adverse effects seem to be unassociated with long-term effects or increased discontinuation of medication in the clinical trials.

Latanoprost currently requires refrigeration prior to dispensing to maintain a 36-month shelf life, while bimatoprost and travoprost do not. The manufacturer of latanoprost has stated their belief that the FDA will eliminate this requirement in early 2003.

Coverage of Clinical Needs: Latanoprost has 95% of the market share in MTFs and 79% in the MHS (MTF, NMOP, and retail). To date there are no studies to show that if one patient fails to respond to one prostaglandin that they will respond to another.

Provider Acceptance: Responses from ophthalmologists agreed that a prostaglandin should be on the BCF. Currently 75% of MTF formularies contain latanoprost, 9% bimatoprost, 4% travoprost, and 2% unoprostone. Providers stated that they are standard second line therapy in the treatment of glaucoma and first line therapy when beta-blockers are contraindicated. Two of the five ophthalmologists preferred latanoprost to other prostaglandins; the other three had no preference. Latanoprost has been on the market longer than the other prostaglandins, so providers have more confidence in its safety profile. Providers were uniformly opposed to a contract that would require patients to be switched from one prostaglandin to another.

Although pilocarpine has low utilization in the MTFs the Council unanimously voted to maintain its BCF status due to its unique place in therapy in the treatment of acute closed angle glaucoma. Timoptic XE has a utilization rate that is consistently higher than the contracted timolol ophthalmic solution, once daily vs. twice daily dosing that may potentially increase compliance, and a current contract price that makes its cost comparable to the ophthalmic solution. The Council unanimously voted to add Timoptic XE to the BCF. The Council voted unanimously to add a prostaglandin to the BCF utilizing a closed class contracting strategy competing latanoprost, bimatoprost and travoprost, which would not require patients to be switched from one agent to another.

10. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Atypical antipsychotics* –In November 2001, the DoD P&T Executive Council removed oral haloperidol from the BCF due to decreasing utilization and the perception that primary care providers in the outpatient setting do not commonly prescribe antipsychotics. The BCF does not currently include any agents approved specifically for the treatment of psychosis.

After considering the following, the Council agreed that one or more atypical antipsychotic agents are needed on the BCF:

- The PEC received two requests from MTF providers to add one or more atypical antipsychotics to the BCF (one for olanzapine and one for olanzapine and risperidone). The requestors argued that: atypicals are first-line agents in treating psychotic manifestations of psychiatric disorders, they are utilized by civilian and military psychiatrists and should be readily available for continuation treatment, and that typical antipsychotics are no longer standard of care for patients who need long-term therapy.
- All eleven MTF providers (10 psychiatrists, 1 internist) who responded to a PEC survey responded “yes” to the following question: “In your opinion, is there a need to make one or more atypical antipsychotic uniformly available across the MHS by adding it or them to the BCF (which would require all MTFs to add them to their formularies)?”

- Utilization of atypical antipsychotics at MTFs is increasing, both in absolute number of prescriptions and relative to prescriptions for typical antipsychotics.
- An analysis of formulary information from 102 MTFs revealed that 69 facilities had at least one atypical antipsychotic on formulary.
- Atypical antipsychotics are termed atypical due to a decreased propensity to induce extrapyramidal side effects (EPS) and decreased risk of tardive dyskinesia relative to typical antipsychotics. Atypical antipsychotics may also be more effective than typical antipsychotics for treating the negative symptoms of schizophrenia and may be effective in patients refractory to typical antipsychotics.
- Atypical antipsychotics are used for multiple conditions besides schizophrenia (e.g., bipolar mania, depression with psychosis, acute agitation in the elderly; symptoms of dementia including agitation, hyperactivity, hallucinations, suspiciousness, hostility and uncooperativeness; bipolar disorder, anxiety disorders, developmental disorders, autism, aggression/self injurious behavior, and Tourette's syndrome), some of which may be treated by primary care providers. In addition, primary care providers may continue medications written by specialists.
- Addition of an atypical antipsychotic to the BCF may foster the recapture of prescriptions from the retail point of service. However, the potential for recapture may be somewhat limited by the fact that civilian providers write about 50% of prescriptions for atypical antipsychotics filled by MTFs. Overall, civilian providers write about 40% of the prescriptions filled by MTFs (based on prescription data from the Uniformed Services Prescription Database).

The Council unanimously approved a recommendation that the PEC complete its review of the atypical antipsychotics and make a specific recommendation to the Council at the next meeting regarding the number of agents that should be added, and which agent(s) represent the most cost-effective choice.

B. *Oral contraceptives* – The BCF does not currently include an oral contraceptive (OC) with low estrogen content (20 mcg ethinyl estradiol [EE]). OCs with low estrogen content have a lower risk of venous thromboembolism and other adverse events. The two monophasic OCs with 20 mcg ethinyl estradiol most commonly used in MTFs are norethindrone/EE/ferrous fumarate 1/0.02 mg and levonorgestrel/EE 0.1/0.02 mg. The brand of norethindrone/EE/ferrous fumarate 1/0.02 mg most commonly used in MTFs is Loestrin FE, which is available at a cost of about $0.21 per cycle. A generic equivalent for Loestrin FE, Microgestin FE, is available but is not currently listed on the FSS. The brand of levonorgestrel/EE 0.1/0.02 mg most commonly used in MTFs is Alesse, which is available at a cost of about $6.03 per cycle. A generic equivalent for Alesse, Aviane, is available but is not currently listed on the FSS. Aviane is the most commonly used product in this category in the retail network and NMOP.

After noting that previous attempts to contract for OCs met with limited success, the Council voted to add norethindrone/EE/ferrous fumarate 1/0.02 mg (Loestrin FE or its generic equivalent) to the BCF.

The Council was also informed that a generic version of ethinyl estradiol 35/norethindrone 0.5/0.75/1 mg oral (Ortho-Novum 7/7/7) is expected to be available early in 2003. The Council has previously discussed the difficulty of obtaining the best price for this product, since lower priced "clinic" packs are available only by direct purchase from the manufacturer, not from Prime Vendor, and the previous depot contract expired at the end of February 2002.

C. *Paroxetine controlled release (Paxil CR)* – Paxil CR is a controlled release formulation of paroxetine that shifts absorption to the small intestine and controls release of paroxetine over 4-5 hours. Because of reduced bioavailability, Paxil CR is formulated as 12.5, 25, and 37.5 mg tablets, which are equivalent to 10, 20, and 30 mg of immediate release paroxetine, respectively. Paxil CR was added to the NMOP formulary in May 2002, but it was not added to the BCF because the information available at that time did not demonstrate that Paxil CR offered any significant advantages compared to Paxil. Paxil CR was to be reviewed again at the November 2002 meeting for potential addition to the BCF.

The clinical trials of Paxil CR for major depressive disorder (MDD) included Paxil treatment arms, but the studies were not designed to compare the efficacy of Paxil CR to the efficacy of Paxil. The clinical trials of Paxil CR for treatment of panic disorder did not include Paxil treatment arms.

Pooled data from MDD trials showed that 23% of Paxil patients and 14% of Paxil CR patients reported nausea during the first week of therapy (a statistically significant difference). Statistically significant differences were not seen in the percentages of patients reporting nausea during weeks 2, 3, 4,or 12 of the trials. According to manufacturer information, the dropout rate in the two adult MDD trials was 6% for placebo, 10% for Paxil CR (non-significant difference), 16% for Paxil (significantly higher than placebo). Paxil CR and Paxil were not directly compared. The percentage of patients dropping out due to nausea was 3.7% in the Paxil CR arm and 0.5% in the placebo arm, but patient dropouts due to nausea were not reported for the Paxil arm.

Provider opinion survey results (12 total; 9 from psychiatry) are summarized as follows:

- 1 “add”
- 6 “don’t add”
- 3 “not sure/no opinion”
- 1 “if replaces Paxil at less cost
- 1 “may be some value; slower release may decrease dizziness, vertigo side effects”

Usage of Paxil CR is increasing in the retail network and NMOP, but very few prescriptions for Paxil CR are filled at MTFs. The FSS prices for Paxil CR and all strengths of paroxetine immediate release except the 40 mg tablet are currently the same: $1.31 per tablet ($1.49 for 40 mg). The prices for Paxil and Paxil CR are similar to FSS prices for other SSRIs, with the exception of the $0.04 contract price for generic fluoxetine 20 mg. It is unclear when a generic version of paroxetine will become available; patent litigation has been in progress since 1998.

The Council concluded that Paxil CR has not been shown to offer any significant clinical advantages over Paxil or other SSRIs on the BCF. The four SSRIs currently on the BCF are more than adequate to meet the clinical needs of DoD beneficiaries. The Council also noted that Paxil CR offers no economic advantage over Paxil or other SSRIs on the BCF and that generic fluoxetine is much less expensive than Paxil CR. Inexpensive generic paroxetine will eventually become available. The addition of Paxil CR to the BCF would likely result in higher costs in the long run, because Paxil CR users would be less likely than Paxil users to switch to generic paroxetine when it becomes available. The Council voted unanimously to exclude Paxil CR from the BCF listing for paroxetine. MTFs are not required to add Paxil CR to their formularies.

D. *Escitalopram (Lexapro; Forest Labs)* – Escitalopram is the S-isomer of citalopram (Celexa; Forest Labs). Citalopram is a racemic mixture (equal amounts of S- and R-citalopram). The s-isomer of citalopram appears to be solely responsible for the antidepressant properties of citalopram. The r-isomer exhibits little binding to serotonin receptors and demonstrates no antidepressant properties. Whether or not the r-isomer results in any clinically significant effect is unclear. Comparable efficacy of 10 mg escitalopram and 40 mg citalopram in clinical trials has led to the theory that the r-isomer may impede binding of the s-isomer at the serotonin receptor or impede receptor function in some other way. The r-isomer does demonstrate affinity for histamine receptors, which could theoretically increase side effects (e.g., sedation) with the racemic mixture compared to the s-isomer alone.

The Committee reviewed escitalopram for addition to the NMOP Formulary in May 2002, just prior to FDA approval. Review of escitalopram for the BCF was tabled until after the drug had been approved by the FDA and was on the market. There are currently four SSRIs on the BCF: citalopram (Celexa); generic fluoxetine - excludes Prozac, Sarafem & Prozac Weekly; paroxetine (Paxil); and sertraline (Zoloft). Forest Labs, which manufactures both citalopram and escitalopram, has ceased promoting citalopram (Celexa), although it will continue to be available. Forest has stated that it does not advocate switching patients who are stable on citalopram or other antidepressants to escitalopram.

Escitalopram is indicated for the treatment of major depressive disorder. The manufacturer's dossier of clinical information for escitalopram includes summaries of the following studies of escitalopram in the treatment of depression:

- Two published 8-week, fixed dose trials, one comparing escitalopram 10 mg to placebo and the other comparing escitalopram 10 mg, escitalopram 20 mg, or citalopram 40 mg to placebo.
- Unpublished data from two 8-week flexible-dose trials comparing escitalopram and citalopram to placebo.
- Unpublished data from a long-term (36 week) extension study
- A published analysis of pooled trial data focusing on anxiety symptoms in depressed patients

Unpublished data addressing the use of escitalopram in generalized anxiety disorder, social anxiety disorder, and panic disorder are also available.

The following table summarizes published efficacy data for escitalopram:

Reference	Trial Design	Primary Endpoint	Results
Burke et al. (J Clin Psych 2002; 63:331-6)	Double-blind, RCT in outpatients aged 18-65 years, with MDD for at least 4 weeks 1-week washout, period, then randomized to 8-week treatment with E10 (n=118), E20 (n=123), C40 (n=125), or placebo (n=119)	Change from baseline in MADRS score at Week 8	Placebo: -9.4 E10: -12.8* E20: -13.9* C40: -12.0*
Wade et al (Int Clin Psycopharmacol 2002; 17(3):95-102)	Double-blind, RCT in primary care patients aged 18-65 years, with MDD for at least 4 weeks 1-week washout period, then randomized to 8-week treatment with E10 (n=191) or placebo (n=189)	Change from baseline to final assessment of MADRS score	Placebo: -13.6 E10: -16.3*
Gorman et al (CNS Spectrums 2002: 7 (suppl 1):40-4)	Pooled data from fixed dose study (E10, E20, C40, placebo) & two flexible dose studies (E10-20, C20-40, placebo) combined n = 1321	Mean change in MADRS score at Week 8	Placebo: -11.2 E: -13.8* C: -13.1*

*p<0.05 vs. placebo
RCT = randomized controlled trial; MDD = major depressive disorder; MADRS = Montgomery Asberg Depression Rating Scale ;E10 = escitalopram 10 mg daily; E20 = escitalopram 20 mg daily; C40 = citalopram 20 mg daily

In the pooled data analysis, two different assessments were evaluated, with two additional analyses of one measure: the Montgomery Asberg Depression Rating Scale (MADRS), the MADRS among patients severely depressed at baseline, the MADRS Inner Tension Item Score, & CGI-I. In each case, the mean change from baseline was determined. For each measure, the mean change from baseline appeared to be significantly different than placebo at earlier time points for escitalopram than for citalopram. Given limited data and the *post priori* nature of the analysis, the existence of a real difference between escitalopram and citalopram with respect to onset of therapeutic effect remains unclear, as do the effect size and clinical importance of any such difference.

Escitalopram appears to have the same generally favorable drug interaction profile as citalopram. Based on available clinical trial data, there is little evidence of differences between the two products with respect to side effect profile. In an 8-week, fixed dose trial (Burke et al) comparing placebo, escitalopram 10 mg, escitalopram 20 mg, and citalopram 40 mg, withdrawal rates due to adverse events were 2.5%, 4.2%, 10.4%*, and 8.8%*, respectively (*p<0.05 vs. placebo). Somnolence occurred in less than 10% of patients in either group.

Provider opinion survey results (12 total; 8 from psychiatry):

- 2 “add”
- 7 “don’t add”
- 1 “too early to tell”
- 1 “add if it’s cheaper”
- 1 “don’t know”

Usage of escitalopram is increasing in the retail network, but very few prescriptions are filled at MTFs or in the NMOP. Forest has offered BPA prices for citalopram and escitalopram. Approval of a generic version of citalopram is not likely until 2005; citalopram’s new molecular entity patent expires July 2003 with a pediatric extension until January 2004.

The Council concluded that escitalopram does not offer significant clinical advantages over citalopram or other SSRIs on the BCF. The four SSRIs currently on the BCF are more than adequate to meet the clinical needs of DoD beneficiaries. The Council also noted that escitalopram offers no economic advantage over citalopram or other SSRIs on the BCF and that generic fluoxetine is much less expensive than escitalopram. Inexpensive generic citalopram will eventually become available. The addition of escitalopram to the BCF would likely result in higher costs in the long run, because escitalopram users would be less likely to switch to generic citalopram when it becomes available. The Council voted unanimously to exclude escitalopram from the BCF. MTFs are not required to add escitalopram to their formularies.

E. *Methylphenidate extended release capsules (Metadate CD)* – The Council reviewed Metadate CD for inclusion on the BCF, secondary to new clinical information and a BPA offer from Celltech Pharmaceuticals in exchange for placement on the BCF. The Council voted not to add Metadate CD to the BCF. The reasons for this decision were:

- The new clinical information presented by Celltech did not demonstrate that Metadate CD was clinically superior to Concerta.
  - The information provided was a summary of unpublished data that was not peer-reviewed.
  - There were concerns about the study design, statistical methods, and reporting of the results.
  - The assessment tools used to demonstrate the statistical superiority of Metadate CD are not routinely used in clinical practice, making it difficult to determine the clinical relevance of the research findings.
  - These assessment tools appeared to show that the active comparator Concerta was more efficacious at 12 hours post dose.
- Concerta was added to the BCF to take advantage of its long duration of action, which hopefully would eliminate the need for additional immediate release (IR) methylphenidate later in the school day. A subsequent analysis of PDTS data revealed that 7% of patients receiving Concerta required additional doses of IR methylphenidate later in the school day, compared to 43% receiving Ritalin SR. The data provided to the Council suggested that Metadate CD has a shorter duration of action than Concerta; some members of the Council were therefore concerned that it would be less effective than Concerta in eliminating the need for additional doses of IR methylphenidate later in the day.
- MTF providers responded negatively to the proposal to add Metadate CD to the BCF.
- The offered prices in the BPA proposal would not provide a substantial cost avoidance. While the daily cost of therapy would be lower for Metadate CD at low doses of medication, Metadate CD would actually still be more expensive at higher doses. Also, this price consideration does not take into account the increased likelihood of having to add afternoon or evening doses of immediate release methylphenidate to the regimen. The Council also felt it would be extremely unlikely that Metadate CD would achieve a 35% market share given that most providers surveyed were very pleased with the once-daily stimulant currently on the BCF (Concerta).

F. *Niacin extended release tablets (Niaspan)* – Since the publication of the National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) last year, increasing focus is placed on positively affecting the entire lipid profile by using statin adjuncts for patients with mixed dyslipidemias. The DoD P&T Executive Council evaluated Niaspan (prescription only, extended–release niacin tablets) shortly after its FDA approval. The result was not to add Niaspan to the BCF at that time because sufficient data did not exist to justify its benefit over niacin immediate release therapy. Niacin immediate release oral (OTC) is currently on the BCF.

Since Niaspan's approval, clinical trials using Niaspan in combination with simvastatin and in type 2 diabetics have been published reinforcing niacin's beneficial effects in these populations. The PEC completed a database analysis assessing the tolerability of Niaspan and immediate release niacin treated patients. Niacin-naïve patients beginning Niaspan or other niacins in January and February of 2002 were identified and included for analysis. Patients remaining on therapy at least 6 months later were deemed a success for this analysis. In the Niaspan group, 55% (1676/3044) of the Niaspan group were successful versus 37% (282/769) of the other niacin group were successful in tolerating niacin therapy using continued therapy as the marker.

Niaspan is currently on approximately 40% of MTF formularies and is also on the VA National Formulary. The drug cost for Niaspan remains significantly more than immediate release niacin (~$0.30/tab of Niaspan vs. $0.02/tab of immediate release niacin). Fibrates are the mostly likely alternative to niacin therapy, and the drug costs are comparable ($0.20-$0.85/day) to Niaspan. Fibrates are better tolerated than niacin, but niacin is more effective at raising HDL and is generally considered less likely to cause myopathy than fibrates. Responses from healthcare providers at MTFs were overwhelmingly in favor of adding Niaspan to the BCF.

The Council concluded that niacin therapy remains a recommended treatment in many dyslipidemias. Niaspan significantly improves patient's ability to remain on niacin compared to older formulations, thus reducing the number of patients requiring less effective, and possibly less safe, alternatives.

The Council unanimously voted to replace immediate-release niacin with Niaspan on the BCF. MTFs may continue to have other niacin products on their formularies.

11. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF DELETION

A. *Guaifenesin extended release tablets* – Based on the following information, the Council voted to remove guaifenesin 600 mg extended release from the BCF. MTFs may decide whether or not to remove the product from their formularies.

- As of 12 July 2002, Mucinex (Adams Labs) became the first single ingredient guaifenesin extended release product to be 1) approved as safe and effective under a New Drug Application (NDA) and 2) to be approved as an over-the-counter (OTC) product.
- The FDA has determined that single ingredient guaifenesin extended release drug products are new drugs and require an approved application for marketing. The Durham-Humphrey Amendment of 1951 to the Food, Drug, and Cosmetic Act (FDCA) forbids simultaneous marketing of products of the same strength, dose, and indication for both OTC and prescription use. Manufacturers can no longer market single ingredient guaifenesin extended release products as prescription drugs. In October 2002, the FDA sent warning letters to manufacturers and distributors explaining that currently marketed single ingredient guaifenesin extended release products without an approved application are considered

misbranded and in violation of section 505(a) of the FDCA. The FDA requested action plans to bring their products into legal compliance. At least one affected manufacturer is known to be petitioning this action, but it is not known if any single ingredient guaifenesin extended release product other than Mucinex will continue to be available in the near future.

- The Council reviewed the issue of OTC coverage on the BCF at the May 2002 meeting. Although TRICARE policy (which limits coverage of OTCs to insulin, diabetic supplies, and vitamins when used as a specific treatment of a medical condition) does not govern the availability of OTC products at MTF pharmacies, the Council has historically refrained from adding OTC products to the BCF. In addition, the Uniform Formulary Proposed Rule states, "The Basic Core Formulary (BCF) is a subset of the Uniform Formulary and is a mandatory component of all MTF pharmacy formularies." If the BCF is to be a subset of the Uniform Formulary, the inclusion of OTCs on the BCF will be limited by TRICARE policy. The Council voted not to add any additional OTC products to the BCF beyond those identified in the TRICARE Policy Manual. The Council encouraged MTFs to continue providing OTC medications when they represent cost-effective alternatives to legend drugs.

As an OTC product, Mucinex will not be available from the retail network or NMOP.

12. MTF REQUESTS FOR BCF CHANGES

A. Requests to add zonisamide (Zonegran) to the BCF – A MTF provider requested the addition of zonisamide to the BCF. The rationale for the request was that zonisamide is a useful and safe drug to use for diabetic peripheral neuropathy, chronic headache syndromes, restless leg syndrome, and chronic back pain. No supporting literature was presented along with the request. CAPT Torkildson performed the analysis and presented the findings to the Council for consideration.

The FDA approved zonisamide in March 2000 as "adjunctive therapy in the treatment of partial seizures in adults with epilepsy". This approval was based on three registration trials that demonstrated statistical and clinical superiority over placebo in treating patients with partial seizures who were inadequately controlled on at least one other antiepileptic drug (AED). There are no data at present supporting its use as monotherapy for partial seizures. Also, despite the statement in the BCF request that zonisamide was useful for the off label indications listed, there are no published data supporting its utility in treating any of the listed conditions. One open-label study was identified that suggested that zonisamide might be of some benefit in treating patients with Parkinson's disease, but this had not yet been confirmed.

Analysis of available safety data raised some concerns. Zonisamide is a sulfonamide derivative, and is contraindicated in patients with an allergy to sulfonamides. Three cases of severe hematologic adverse events (2 cases of aplastic anemia, 1 case of agranulocytosis) have been reported in Japan, where the drug has been on the market for approximately 10 years. Based on the number of patient-years of exposure, the frequency of this adverse event is higher than that observed in the general population. Several cases of oligohydrosis and hyperthermia have been reported in pediatric patients treated with this agent; the FDA added a bolded warning to the package insert in June 2002 notifying prescribers of this concern. Additionally, 4% of 991 patients treated with the drug during its development phase developed renal stones, and in several studies it was noted that patients treated with zonisamide had a mean increase in their BUN and creatinine of 8%, compared to essentially no change in the placebo group. Of particular concern was the fact that these values did not return to baseline following discontinuation of the drug.

Regarding tolerability, it was noted that in several controlled trials the discontinuation rate due to adverse events in the zonisamide group was twice that of the placebo group (12% vs. 6%), while a separate analysis of several trials with a total of 1,336 treated patients revealed that 21% of patients discontinued therapy due to adverse events.

Finally, a utilization analysis revealed that only 61 MTFs filled prescriptions for zonisamide in FY02, only 23 MTFs filled more than 6 zonisamide prescriptions in that year, while 26 sites filled 3 or fewer. During that same period a total of 3,800 prescriptions for zonisamide were filled in the retail network.

Based on this review, the PEC concluded that there was insufficient evidence to support the use of zonisamide for the conditions outlined in the BCF request. Additionally, the level of concern regarding safety is higher for zonisamide than for other products, such as gabapentin, used for the treatment of these conditions. Gabapentin was added to the BCF in August 2002, providing uniform availability of a similar product with a more acceptable safety and efficacy profile. Finally, the overall utilization of this product across the MHS appears insufficient to require all facilities to make this product available. The PEC recommended that zonisamide not be added to the BCF. The Council unanimously approved this recommendation.

B. *Request to add pimecrolimus (Elidel) to the BCF–* A MTF provider requested that pimecrolimus, a topical immunomodulator (TIM), be added to the BCF. This is a new class of topical, nonsteroidal medications indicated for the treatment of atopic dermatitis (AD). Tacrolimus (Protopic) has been available since December 2000, and is FDA approved for treatment of moderate to severe atopic dermatitis. Pimecrolimus (Elidel) has been available since early 2002, and is FDA approved for the treatment of mild to moderate atopic dermatitis. Atopic dermatitis starts in early childhood and causes significant quality of life issues related to the pruritis and appearance of the rash. Ninety percent of AD patients have mild to moderate severity of disease and the rest are moderate to severe.

Efficacy: Randomized-controlled trials demonstrate that both agents are more efficacious than placebo in the treatment of AD. Tacrolimus appears to be as efficacious as a medium potency topical corticosteroid, where pimecrolimus is as efficacious as a low potency topical corticosteroid.

Safety/tolerability: Neither drug has clinically significant adverse effects, which cause the patients to discontinue use. The drugs are not systemically absorbed, so can be used long term without the worries associated with long-term topical corticosteroids (CS) use. They can also be used in sensitive body areas such as the face and intertriginous regions where one would not want to use topical CS.

Other: Provider response was markedly positive regarding the potential of having an alternative to topical steroids for patients that require one. At the same time, providers noted that these will not take the place of the low potency topical CS and the usual initial therapies for mild AD. Pimecrolimus prescription fills in all points of service (MTF, NMOP, and retail) are increasing, with the majority of its use in the very young (ages 0 - 4) and elderly (ages 65+) population. Providers feel that usage will continue to increase significantly in this class.

The Council agreed that topical immunomodulators (TIMS) are a unique class and have a substantial place in therapy for the treatment of AD, however there is concern regarding the cost of these agents and the potential for misuse. The Council agreed to consider one or both of these medications for addition to the BCF at their next meeting. They asked the PEC to explore procurement options and report back in three months.

13. DEPLOYMENT FORMULARY AND SUPPORTING HOMELAND SECURITY (JRCAB) – LTC Marc Caouette presented information and a short brief on homeland security and deployment formulary to the DoD P&T Executive Council.

14. ADJOURNMENT

The meeting adjourned at 1530 hours on 20 November 2002. The next meeting will be held at Fort Sam Houston, TX at 0800 on Wednesday, 6 March 2003. All agenda items should be submitted to the co-chairs no later than 14 February 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

APPENDIX A: BISPHOSPHONATE CLINICAL EFFICACY: CLINICAL TRIAL RESULTS

Table 1

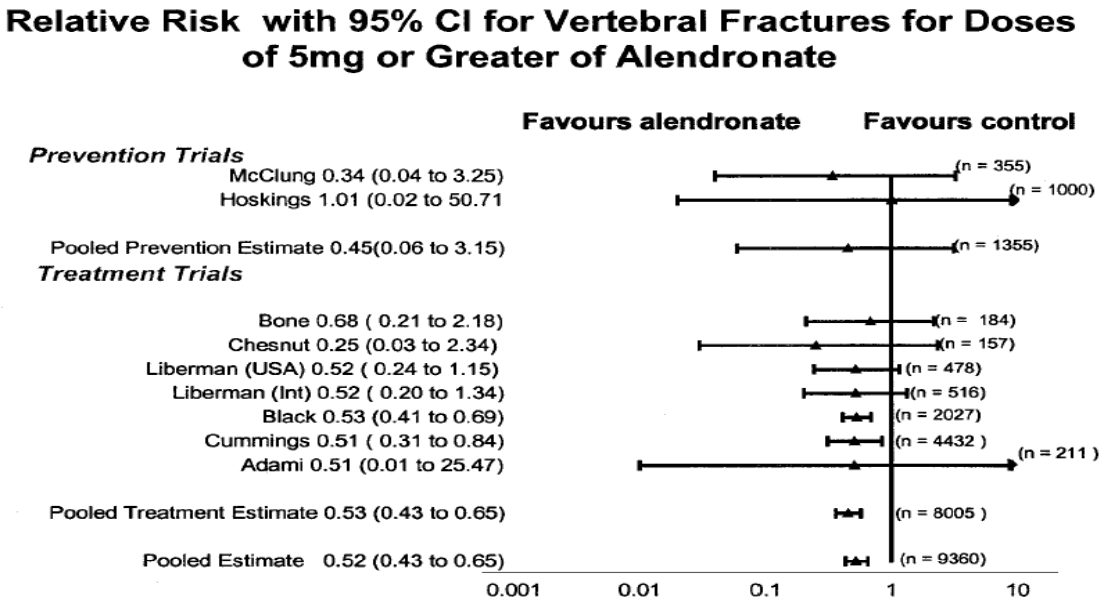


FIG. 2. RR for vertebral fractures with alendronate (5 mg and greater).

From Cranney et al; Endocrine Reviews 2002; 23(4):508-516

Table 2

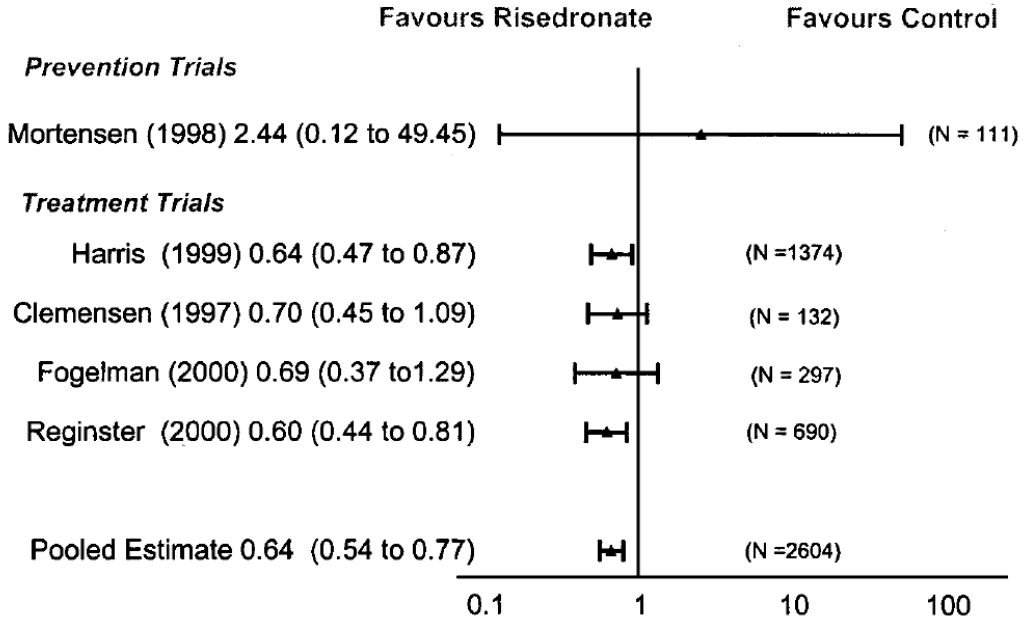


FIG. 2. Relative risk with 95% CI for vertebral fractures after treatment with risedronate.

From: Cranney et al; Endocrine Reviews 2002; 23(4):517-523

Table 3

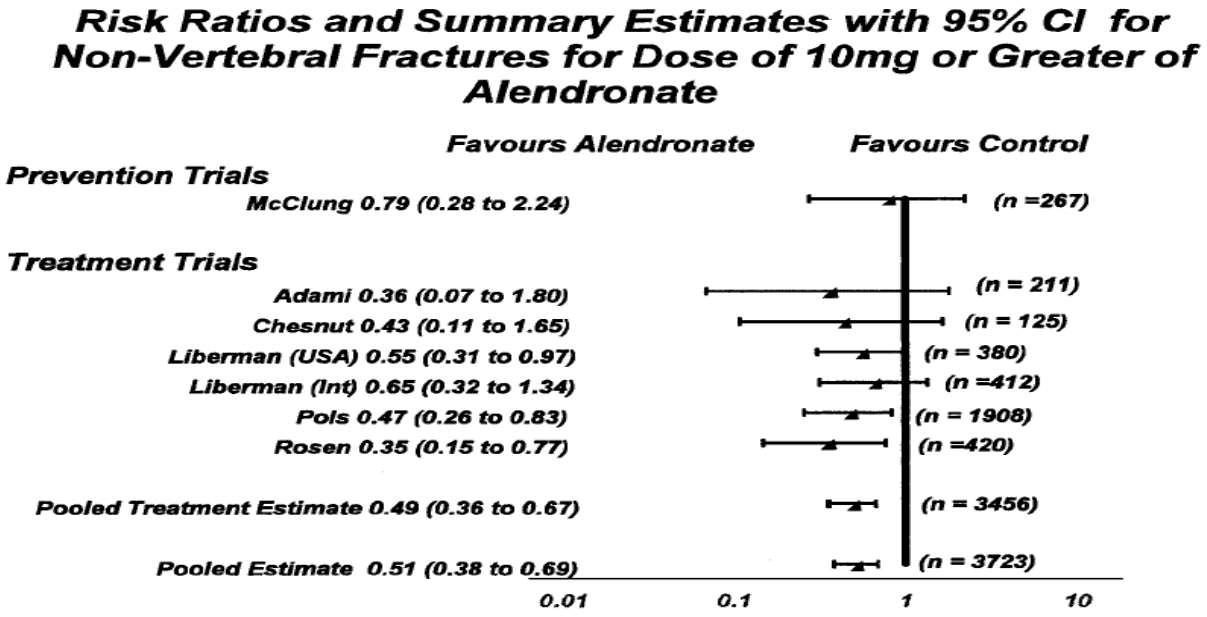


FIG. 3. Risk ratios for nonvertebral fractures with alendronate (10 mg and greater).

From: Cranney et al; Endocrine Reviews 2002; 23(4):508-516

Table 4

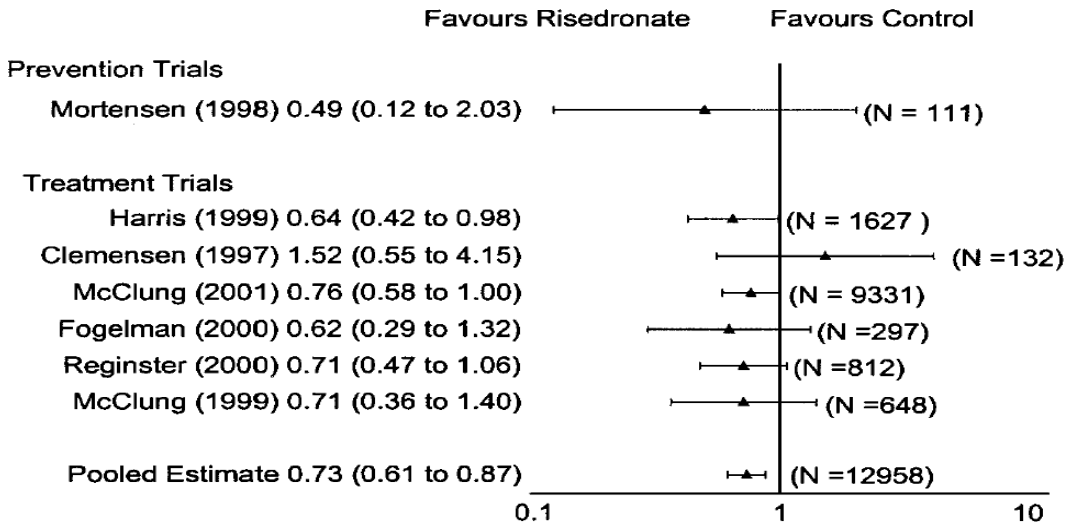


FIG. 3. Relative risk with 95% CI for nonvertebral fractures after treatment with risedronate.

From: Cranney et al; Endocrine Reviews 2002; 23(4):517-523

Table 5 – Summary of Reviewed Bisphosphonate Clinical Trials for Hip Fracture Outcomes

Study*	N	Incidence**	% Risk Reduction	Absolute Risk Reduction	NNT	Significance
Cummings [A] - 4yrs	4,432	A: 0.9% P: 1.1%	18%	0.002	500	No (P=0.44)
Liberman [A] – 3yrs	994	A: 0.2% P: 0.8%	75%	0.006	200	Not powered
Black [A] – 3yrs	2,027	A: 1.1% P: 2.2%	50%	0.011	91	Yes (P=0.047)
McClung [R] – 3 yrs	9,331	R: 2.8% P: 3.9%	28%	0.011	91 (29-333)	Yes (all) (P=0.003)
Harris [R] – 3yrs	1,628	R: 1.5% P: 1.8%	17%	0.003	333	Not powered
Reginster [R] – 3 yrs	814	R: 2.2.% P: 2.7%	19%	0.005	200	Not powered

* Lead author's last name, active component ([A]=alendronate and [R]=risedronate) and study duration
** A=Alendronate, R=Risedronate, P=Placebo

Adapted from Bolognese; The Endocrinologist 2002; 12:29-37

APPENDIX B: PROSTAGLANDIN CLINICAL EFFICACY - HEAD-TO-HEAD COMPARISON TRIALS

Table 1: Latanoprost vs. Unoprostone

Trial	Study Design	Latanoprost	Unoprostone	Duration	N	Baseline IOP (SEM)		End point IOP Reduction1 (SEM)	
						L	U	L	U
Tin Aung 2001	Randomized double-masked crossover	0.005% once daily	0.12% twice daily	2 tx periods of 1 month separated by a 3 week washout period	56	22.3 (0.5)	23.2 (0.4)	6.1 (0.5) p<.001	4.2 (0.4) p<.001

L = latanoprost, U = unoprostone, IOP = intraocular pressure
The difference of 1.9 mmHg between treatments was statistically significant in favor of latanoprost (p = .003, ANCOVA)

Table 2: Latanoprost vs. Travoprost

Trial	Study Design	L	TR	T	Duration	N	Mean Baseline IOP			Mean End point IOP		
							L	TR	T	L	TR	T
Netland 2001	Randomized multicenter, double-masked active-controlled, parallel	0.005% once daily n = 194	0.0015% n = 201 and 0.004% n = 196 once daily	O.5% Twice daily N = 196	12 months	787	25.7	25.1 (0.0015%) 25.5 (0.004%)	25.7	18.7	18.6 (0.0015%) 18.6 (0.004%)	20.2

L = Latanoprost, TR = Travoprost, T = timolol, IOP = intraocular pressure
Baseline and end point IOP difference between timolol and travoprost was statistically significant for both strengths (p<0.001, ANOVA)
Baseline and end point IOP difference between travoprost (both strengths) and latanoprost were statistically insignificant at alpha = 0.05

Table 3: Latanoprost vs. Bimatoprost

Trial	Study Design	L	B	Duration	N	Mean Baseline IOP Range		Mean End point IOP	
						L	B	L	B
Gandolfi 2001	Randomized multicenter, investigator-masked, parallel group trial	0.005% n = 113 once daily	0.03% n = 119 once daily	Three month	232	22.4 to 25.7	22.6 to 25.7	17.4 to 18	17 to 17.5
Trial	**Study Design**	**L**	**B**	**Duration**	**N**	**8 AM Mean Baseline IOP (SEM)**		**Reduction in IOP from baseline at day 29**	
						L	**B**	**L**	**B**
DuBiner 2001	Multicenter, double-masked, randomized, clinical trial	0.005% n = 21 once daily	0.03% n = 21 once daily	30-days	63	25.2 (0.6)	25.6 (0.5)	4.4 – 7.6 20-30%	5.9 – 8.0 25.4–30.9%
		Vehicle n = 21				Vehicle 25.8 (0.6)		Vehicle -0.3 – 1.7 -2 – 6.5%	

L = latanoprost, B = bimatoprost, IOP = intraocular pressure
Gandolfi: Mean IOP was lower with bimatoprost than with latanoprost at all time points (8AM, 12, 4PM, 8PM) during the three month follow-up, although the between group difference was not always statistically significant.
DuBiner: Bimatoprost and latanoprost significantly lowered IOP from baseline (p<0.001). Bimatoprost lowered IOP more than latanoprost at every time point measured, although the between group differences did not reach statistical significance.

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MCCS-GPE **8 AUGUST 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 8 August 2002, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC, USN	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS, USA	DoD P& T Committee Co-chair
COL Mike Heath, MS (Representing MAJ Brett Kelly, MS)	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
Col Bill Sykora, MC	Air Force
COL Ardis Meier, BSC (Representing LtCol George Jones, BSC)	Air Force Pharmacy Consultant
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs

VOTING MEMBERS ABSENT

COL Rosa Stith, MC	Army
Col John R. Downs, MC	Air Force
LTC (P) Joel Schmidt, MC	Army

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, USAF, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
Maj Barb Roach, USAF, MC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
HM1 Lisa Drumm, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
David Chicoine	Uniformed Services Family Health Plan
Mark Petruzzi	Medco Health
Ron McDonald	Sierra Military Health Services
Kelly Lenhart	Humana
William Hudson	Humana
Gene Lakey	TriWest
Ray Nan Berry	Health Net Federal Services
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)

3. **REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **INTERIM DECISIONS** – No interim decisions.

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL Davies reported that the comment period for the UF proposed rule has closed. The TMA Pharmacy Program Office is currently in the process of formulating responses to comments submitted by the public.

6. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 5 new drugs or formulations (see Appendix A). The PEC also presented brief information on six additional new drugs or formulations not felt to require a complete review by the Committee. The Committee agreed that no further review was required (see Appendix B for comments).

7. NMOP AND RETAIL NETWORK ISSUES

A. Clarification of the NMOP quantity limits for antibiotics – LtCol Ed Zastawny (PEC) reported on a re-evaluation of the 30-day quantity limit that the DoD P&T Committee established in July 1998 for antibiotics dispensed through the NMOP. The Committee agreed that providers are unlikely to prescribe large quantities of antibiotics unless the patient needs long-term antibiotic therapy. The 30-day quantity limit increases the administrative burden for patients with a legitimate need for long-term antibiotic therapy because they have to reorder medication more frequently. More frequent reordering of medication also increases the risk that patients will run out of medication. Patients' costs are higher because they have to pay more copays.

The Committee concluded that the 30-day quantity limit probably creates more problems than it prevents and unanimously voted to eliminate the 30-day quantity limit on antibiotics in the NMOP. Antibiotics will be dispensed according to the general rule applied to other drugs in the NMOP (up to a 90 day supply). Existing quantity limits for specific antibiotics will remain in force. All quantity limits will be posted on the quantity limit page on the PEC website.

B. Clarification of the NMOP quantity limits for myeloid stimulants, interferon gamma, interferon alpha, and sandostatin injection – The current NMOP quantity limit for these products is 30 days. Because literature supports chronic use of the interferons and sandostatin for specific indications, the Committee unanimously voted to remove the 30-day quantity limit from interferon alpha, interferon gamma, and sandostatin. The Committee agreed that a 30-day quantity limit on myeloid stimulants was reasonable given the products' indications and uses. They noted that the NMOP quantity limit for PEG-filgrastim was set at 2 syringes per 45-day supply at the May 2002 meeting. The Committee voted to retain the 30-day quantity limit for myeloid stimulants, except for PEG-filgrastim, which will remain as 2 syringes per 45-day supply limit. The quantity limits will be posted on the PEC website quantity limit page. The NMOP will not use quantity limits other than those listed on the PEC website and will revise their database(s) accordingly.

C. Clarification of NMOP quantity limits for testosterone transdermal patches (Androderm) – Current NMOP quantity limit for Androderm patches is 30 days. Testosterone topical gel (Androgel) has a NMOP quantity limit of 90 days. Both are chronic replacement products with low abuse potential. The Committee voted unanimously to remove the 30-day quantity limit on all topical/transdermal testosterone or androgen replacement products.

8. COST AVOIDANCE FROM NMOP PRIOR AUTHORIZATIONS (PAs) –Shana Trice reported on the estimated cost avoidance due to PAs in the NMOP. The cost avoidance per prescription is based on the cost avoidance model that was outlined in the Aug 00 DoD P&T Committee minutes. The Committee did not make any changes to these PAs.

Drug	2nd Quarter FY 02	3rd Quarter FY 02
Sildenafil	$11.54	-$7.79
COX-2 inhibitors	$4.10	$2.65
Etanercept	$62.84	$15.30
Anakinra	-	$1132.00

Note: Cost avoidance due to the PA for antifungals for onychomycosis (ciclopirox, itraconazole, terbinafine) is not calculated using this model because the PA differs substantially from the other PAs. Unlike the other PAs, which authorize dispensing of new and refill prescriptions for a year, each course of therapy with antifungal medications for the treatment of onychomycosis goes through the PA process.

9. SUBCOMMITTEE REPORT: PROVISION OF INJECTABLE DRUGS IN THE NMOP OR RETAIL NETWORK PHARMACIES – At the May 2002 meeting the Committee asked the PEC to analyze the prescriptions filled in the retail network for injectable drugs to determine if there were additional drugs that should be added to the NMOP Covered Injectables List. CAPT Torkildson reported on the results of that analysis.

A report was generated from PDTS listing all prescriptions filled for injectable drugs in the retail network and at the NMOP during the period 1 April 2001 – 3 May 2002. Prescriptions for drugs currently included on the NMOP Covered Injectables List were then excluded. Remaining prescriptions were then sorted based on volume of prescriptions filled and total cost to the government. The greatest volume of prescriptions filled for non-list items was for methotrexate, with 3,072 prescriptions filled over 12 months. No other non-listed medication had greater than 1,000 prescription fills. In contrast, over 39,000 prescriptions for NPH insulin, which is on the covered injectables list, were filled at retail pharmacies during the surveyed period. The drug with the highest total submitted cost due was colistimithate, with a total due of $65,792. Only colistimithate and hydromorphone had costs greater than $50,000. In contrast, the retail network cost for epoetin alpha, which is on the covered injectables list, was almost $5.9 million over the same period.

The Committee decided to add dihydroergotamine 1 mg/ml, heparin sodium 5,000 & 10,000 units/ml, and promethazine 25 mg/ml to the NMOP Covered Injectables List. Because other migraine medications are subject to quantity limits and because use of dihydroergotamine should not exceed 6 ampules per week for safety reasons, the Committee established a quantity limit for dihydroergotamine: 3 boxes (30 ampules) per 30 days in the retail network and 9 boxes (90 ampules) per 90 days in the NMOP.

The Committee also recognized that a substantially greater opportunity for cost avoidance hinged on a more aggressive use of the NMOP by patients and providers to fill prescriptions for injectable drugs already available at the NMOP.

10. **CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS** – All the Managed Care Support Contractors have established network agreements with CVS Procare Specialty Pharmacy, making CVS Procare the preferred site for DoD patients to obtain drugs requiring controlled distribution. The current plan is to use CVS Procare, whenever possible, for future drugs requiring controlled distribution. Information about specific drugs is available on the PEC website.

11. **ADJOURNMENT –** The meeting adjourned at 1100 hours. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland starting at 0800 on Thursday, 21 November 2002. All agenda items should be submitted to the co-chairs no later than 18 October 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP and/or retail network formulary restrictions	BCF Status
Voriconazole (Vfend; Pfizer)	29 May 02; Treatment of invasive aspergillosis primarily due to *Aspergillus fumigatus* and treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium spp*., including *Fusarium solani* in patients intolerant of, or refractory to, other therapy.	Oral 50 mg and 200 mg tablets were added to the NMOP Formulary; IV formulation was excluded (not for self-administration)	**Quantity Limits** General Rule applies **Prior Authorization:** None	Not added to the BCF **Similar BCF Drugs:** None. Fluconazole 150 mg for vaginal candidiasis has a different spectrum of activity
Etonogestrel / ethinyl estradiol vaginal ring (Nuva-Ring; Organon)	01 Oct 01; Vaginal ring composed of an estrogen and progestin indicated for the prevention of pregnancy.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** None
Methylphenidate long-acting capsules (Ritalin LA; Novartis)	06 Jun 01; for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6 to 12 years of age	Added to the NMOP Formulary **Note**: Schedule II controlled substance; would fall under standard rule in NMOP for Schedule II products for treatment of ADHD (90 days supply, no refills)	**Quantity Limits** NMOP: General rule for Schedule II controlled substances for treatment of ADHD applies. (90 days supply, no refills) **Prior Authorization** None	Not added to the BCF. Excluded from the current BCF listing for methylphenidate. **Similar BCF Drugs:** Methylphenidate extended release (Concerta)
Escitalopram (Lexapro; Forest)	Approvable at time of Committee meeting – FDA approval imminent (note: approved by the FDA 14 Aug 02); single-isomer formulation of the selective serotonin reuptake inhibitor citalopram (Celexa)	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF. Will reconsider possible BCF addition following formal FDA approval & availability of pricing information. **Similar BCF Drugs:** fluoxetine, paroxetine, sertraline, citalopram
Lovastatin extended-release tablets (Altocor; Andrx/Aura	27 Jun 02 (will not be marketed until Sept 02); indicated for use in addition to dietary restrictions to lower total cholesterol and LDL cholesterol; and to slow the progression of coronary atherosclerosis in patients with coronary heart disease. Also has indication for primary prevention of CHD in patients with elevated cholesterol (based on the AFCAPS/TexCAPS study).	Not added to the NMOP Formulary. Existence of the current statin contract precludes addition of Altocor to the NMOP formulary.	**Quantity Limits** N/A **Prior Authorization** None	Not added to the BCF. Existence of the current statin contract precludes addition of Altocor to the NMOP formulary.

APPENDIX B: NEWLY APPROVED DRUGS NOT REQUIRING FULL REVIEW BY THE P&T COMMITTEE.

Generic (Trade name; manufacturer)	**Indication**	**Comments**
Desloratadine orally disintegrating tablets (Clarinex Redi-tabs; Schering)	Treatment of allergy symptoms and chronic idiopathic urticaria	Line extension. Desloratadine tablets are already available; both formulations will be available from the NMOP. Consideration for the BCF precluded by current non-sedation antihistamine contract.
Fulvestrant for injection (IM) (Faslodex; Astra-Zeneca)	Treatment of hormone-receptor metastatic breast cancer in postmenopausal women	Not considered for the NMOP Formulary since the IM injection is not designed for self-administration.
Human insulin (rDNA origin) for injection (SC) in a 3 mL disposable prefilled syringe (InnoLet; NovoNordisk)	Human insulin (Novolin) in a 3 mL disposable prefilled syringe	Will be available from the NMOP. Existing BCF listings for Novolin insulin are for 10mL vials. MTFs may decide whether or not to add InnoLet or other alternative insulin delivery devices (e.g., insulin pens) to their formularies.
Treprostinol Na for Injection (Remodulin; United Therapeutics)	Continuous SC infusion for treatment of pulmonary hypertension with NYHA class II-IV symptoms	Restricted drug distribution
Urofollitropin for Injection (Bravelle; Ferring)	Fertility agent	Will be added to the NMOP Covered Injectables List, which already includes other brands of urofollitropin.
Ziprasidone for Injection (IM) (Geodon IM; Pfizer)	Acute episodes of paranoia, and schizophrenia	Not considered for the NMOP Formulary since the IM injection is not designed for self-administration. Emergent use agent not appropriate for the BCF.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

A. Additions to the BCF

1) Venlafaxine extended release capsules (Effexor XR) - contingent on signing of BPA (see Paragraph 10A)
2) Insulin glargine injection (Lantus)
3) Gabapentin (Neurontin)
4) Budesonide inhalation solution (Pulmicort Respules)
5) Meloxicam tablets (Mobic)
6) D, L-amphetamine 10-, 20-, 30-mg extended release capsules (Adderall XR)

B. Deletions from the BCF

1) Cimetidine oral
2) Methylphenidate SR (sustained release) tablets were removed from the BCF listing for methylphenidate.

C. Changes and clarifications to the BCF

1) The current BCF listing for methylphenidate was clarified to specify the following strengths for methylphenidate extended release (Concerta): 18-, 27-, 36-, and 54-mg
2) Existing BCF listings for Novolin insulin are for 10 ml vials. MTFs may decide whether or not to add alternative insulin delivery devices (e.g., insulin pens, InnoLet) to their formularies.
3) Precision products remain the only blood glucose strips on the BCF. MTFs are encouraged to transition to the newer Precision product, Precision Extra, as soon as possible.

D. Exclusions from the BCF

1) Methylphenidate long acting capsules (Ritalin LA, Novartis) were excluded from the BCF listing for methylphenidate.
2) Lovastatin extended-release tablets (Altocor; Andrx/Aura) – existing statin contract precludes addition to the BCF

2. **NMOP FORMULARY CHANGES**

A. *Additions to the NMOP Formulary*

1) Voriconazole 50- and 200-mg tablets (Vfend; Pfizer); injectable formulation not added since it is not for self-administration
2) Etonogestrel/ethinyl estradiol vaginal ring (Nuva-Ring; Organon)
3) Methylphenidate long acting capsules (Ritalin LA; Novartis) – General NMOP rule for schedule II controlled substances for treatment of ADHD applies (90 days supply; no refills)
4) Escitalopram tablets (Lexapro; Forest)

5) Bravelle brand of urofollitropin added to the NMOP Covered Injectables List, which already includes other brands of urofollitropin

6) Dihydroergotamine 1 mg/ml injection added to the NMOP Covered Injectables List

7) Heparin sodium 5,000 & 10,000 units/ml injection added to the NMOP Covered Injectables List

8) Promethazine 25 mg/ml injection added to the NMOP Covered Injectables List

9) InnoLet brand of human insulin for injection (3 mL prefilled syringes) added to the NMOP Covered Injectables List

B. *Exclusions from the NMOP Formulary*

1) Lovastatin extended-release tablets (Altocor; Andrx/Aura) – Existing statin contract precludes addition to the NMOP Formulary.

C. *Clarifications to the NMOP Formulary* - None

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**

A. Quantity limit for dihydroergotamine 1 mg/ml injection: 3 boxes (30 ampules) per 30 days in the retail network, 9 boxes (90 ampules) per 90 days in the NMOP.

B. NMOP 30-day quantity limit for antibiotics was eliminated. Antibiotics will be dispensed consistent with the general rule applied to all other drugs in the NMOP (up to a 90 day supply), unless otherwise specified on the quantity limit page on the PEC website.

C. NMOP 30-day quantity limits for interferon alpha, interferon gamma, and sandostatin were removed. The quantity limit for myeloid stimulants remains 30 days, with the exception of PEG-filgrastim, which has a quantity limit of 2 syringes per 45 days in the NMOP, and 1 syringe per 21 days in the retail network.

D. NMOP 30-day quantity limit for topical/transdermal testosterone or androgen replacement products was removed.

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)** - None

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MCCS-GPE **7 August 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1430 hours on 7 August 2002 at the Uniformed Services University of the Health Sciences, Bethesda, Maryland

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Mike Heath, MS (Representing MAJ Brett Kelly, MS)	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
COL Ardis Meier, BSC (Representing LtCol George Jones, BSC)	Air Force Pharmacy Consultant
CAPT Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs

VOTING MEMBERS ABSENT

COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
HM1 Lisa Drumm, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
Alexandra Masterson, Pharm.D.	Dewitt Army Hospital, Ft. Belvoir, VA

3. REVIEW MINUTES OF LAST MEETING/ADMINISTRATIVE ISSUES

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS – None

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

Contract awards, renewals, and terminations

- New joint DoD/VA contracts were awarded for benztropine, carbidopa/levodopa IR, famotidine, digoxin, indomethacin, metformin, captopril, paclitaxel, trazadone, and chlorhexidine.
- The following joint DoD/VA contracts were not awarded because the bid prices were higher than existing FSS prices: prednisone and cimetidine.
- The following joint DoD/VA contracts are in various stages of solicitation: penicillin, dicloxacillin, tretinoin cream, amoxicillin, and cephalexin.
- The following joint DoD/VA contracts were extended: salsalate and all Geneva generics.

6. EXPIRATION OF LISINOPRIL CONTRACT

LCDR Briski provided information concerning the availability and pricing of lisinopril within the direct care system. The DoD contract with Astra Zeneca that provided the Zestril brand of lisinopril at $0.14 per tablet expired on 31 July 2002. Astra-Zeneca refused a DoD request to extend the Zestril contract. The VA's contract with Merck for the Prinivil brand of lisinopril expires 19 October 2002. Astra-Zeneca and Merck are phasing out production of lisinopril. Although several companies market generic versions of lisinopril, none are listed on the Federal Supply Schedule, and all are priced significantly higher than $0.14 per tablet. The DoD and VA are seeking a joint contract for a generic version of lisinopril, but that contract will not be awarded until after the VA's

Prinivil contract expires. MTFs will probably have to pay higher prices for lisinopril until the contract for a generic version of lisinopril is awarded—hopefully by November 2002.

7. PENDING CONTRACT INITIATIVES

A. *Status of contracting initiatives for Leutinizing Hormone Releasing Hormone (LHRH) agonists, nasal corticosteroids, triptans, and quinolones* – The joint DoD/VA solicitations for these items are still pending.

B. *Status of contracting initiative for Angiotensin Receptor Blockers (ARBs)* – In order for DoD to potentially join the VA in seeking a closed class contract for an ARB, LCDR Briski asked the Council to reconsider its May 2002 decision that the procurement strategy must leave the ARB class "open" on the BCF. The Council's decision not to support a closed class contract centered on concerns about therapeutic interchangeability and clinical coverage for treating congestive heart failure (CHF) and preventing the progression of renal disease in type 2 diabetics.

   The Council considered new information about the extent to which ARBs are prescribed at MTFs for conditions other than hypertension. An analysis of data from the Uniformed Services Prescription Database (USPD) and the M2 (formerly known as the ARS Bridge) database found ICD-9 codes consistent with a diagnosis of CHF or type 2 diabetic renal disease for only 289 (5%) of 5,680 patients who were prescribed two or more daily doses of an ARB (Note: patients with CHF are more likely to be prescribed multiple daily doses of an ARB than patients who are being treated for hypertension). The Council concluded that a closed class contract would be acceptable because the usage of ARBs for these conditions is low enough that MTFs could use the non-formulary request process to provide non-contracted ARBs to patients in the event that the contracted ARB does not meet the clinical needs of patients with CHF or type 2 diabetes. The Council voted unanimously to expand the authorized procurement strategies for the ARB class to include a closed class contract that does not mandate that patients be switched from non-contracted ARBs to the contracted ARB.

C. *Status of contracting initiative for thiazolidinediones (TZDs, "glitazones")* – In order for DoD to potentially join the VA in seeking a closed class contract for a TZD, LCDR Briski asked the Council to reconsider its May 2002 decision that the procurement strategy must leave the TZD class "open" on the BCF. The Council's decision not to support a closed class contract stemmed from concerns that rosiglitazone and pioglitazone may differ significantly in their effects on LDL-cholesterol (LDL-C) levels. The Council considered the results of (1) a more extensive analysis of changes in LDL-C levels reported in clinical trials of TZDs, and (2) an analysis of concomitant statin therapy for DoD patients who were newly started on TZD therapy.

   Comparison of changes in LDL-C levels in clinical trials of TZDs: There are no head-to-head trials that compare the changes in LDL-C levels that are associated with the use of rosiglitazone and pioglitazone. In order to compare the changes in LDL-C levels while attempting to control for known and unknown variations that exist across clinical trials of TZDs, the PEC calculated the percentage change in LDL-C incremental to placebo in nine rosiglitazone trials and five pioglitazone trials. As shown in Tables 1 and 2 below, the incremental percentage increases in LDL-C are consistently larger for rosiglitazone than pioglitazone.

Table 1: Monotherapy trials with TZDs and corresponding LDL changes, incremental to placebo

Rosiglitazone				Pioglitazone			
Dose (N)	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**	**Dose (N)**	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**
Patel				Aronoff			
2 mg bid (79)	125	↑ 13.6%	**↑ 12.4%**	30 mg qd (87)	136	↑ 5.2%	**↑ 0.42**
Placebo (74)	130	↑ 1.2%		Placebo (79)	139	↑ 4.8%	
Lebovitz				Study 026			
2 mg bid (166)	121	↑13.7%	**↑ 8.9%**	30 mg qd (100)	126	↓ 7%	**↓ 7%**
Placebo (158)	121	↑ 4.8%		Placebo (93)	133	No change	
Phillips				Study 012			
2 mg bid (186)	130	↑ 9.5%	**↑ 7.8%**	30 mg qd (85)	123	↑ 7%	**↑ 1%**
Placebo (173)	127	↑ 1.7%		Placebo (83)	135	↑ 6%	
Phillips							
4 mg qd (181)	125	↑ 10.6%	**↑ 8.9%**				
Placebo (173)	127	↑ 1.7%					
Lebovitz				Aronoff			
4 mg bid (169)	124	↑ 18.6%	**↑ 13.8%**	45 mg qd (80)	127	↑ 6%	**↑ 1.2%**
Placebo (158)	121	↑ 4.8%		Placebo (79)	139	↑ 4.8%	
Phillips				Study 012			
4 mg bid (187)	135	↑ 14.3	**↑ 12.6%**	45 mg qd (85)	133	↑ 8%	**↑ 2%**
Placebo (173)	127	↑ 1.7%		Placebo (83)	135	↑ 6%	
Phillips							
8 mg qd (181)	129	↑ 18.3%	**↑ 16.6%**				
Placebo (173)	127	↓ 1.7%					

Table 2: TZD trials in combination with a sulfonylurea or metformin and corresponding LDL changes, incremental to placebo

Rosiglitazone				Pioglitazone			
Dose (N)	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**	**Dose (N)**	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**
Wolffen				Kipnes			
2 mg bid +SU (183)	139	↑ 6%	**↑ 6%**	30 mg qd +SU (189)	127	↑ 6.6%	**↓ 0.4%**
Placebo + SU (192)	139	No change		Placebo +SU (187)	124	↑ 7%	
Study 079							
2 mg bid + glyb (98)	125	↑ 10.4%	**↑ 10.2%**				
Glyb (99)	125	↑ 0.24%					
Study 079							
2 mg bid (99)	125	↑ 17.6%	**↑ 17.4**				
Glyb (99)	125	↑ 0.24%					
Study 096							
4 mg qd + glyb (116)	122	↑ 14.8%	**↑ 12.4%**				
Placebo (115) + glyb	122	↑ 2.4%					
Fonesca*				Einhorn*			
4 mg qd + met (119)	115	↑ 15.4%	**↑ 12%**	30 mg qd +met (161)	119	↑ 7.7%	**↓ 4.2%**
Met + placebo (116)	117	↑ 3.4%		Placebo +met (149)	118	↑ 11.9%	
Fonesca*				No combination trials with 45 mg pioglitazone			
8 mg qd + met (113)	112	↑ 18.7%	**↑ 15.3%**				
Met + placebo (116)	116	↑ 3.4%					

SU = sulfonylurea, glyb = glyburide, met = metformin
*Concomitant lipid-lowering drugs were allowed

Analysis of concomitant statin therapy among DoD patients newly started on TZD therapy: Using data from the Pharmacy Data Transaction Service (PDTS), the PEC identified 14,301 patients who began therapy with rosiglitazone or pioglitazone between 1 November 2001 and 28 February 2002 and analyzed their concomitant statin usage through 30 June 2002. The PEC identified patients who had received prescriptions for statins before starting their TZD therapy, patients who initiated statin therapy after starting TZD therapy, and patients who experienced an increase in the dosage of their pre-existing statin therapy. Table 3 shows that the percentages of patients who were on statin therapy at baseline, were started on a statin, or whose statin dose was increased are very similar for rosiglitazone and pioglitazone.

Table 3: Statin use in DoD patients newly started on TZDs

	Rosiglitazone (n=8369)	Pioglitazone (n=5932)
Statin therapy change	**2120 (25.3%)**	**1371 (23.1%)**
Statin started after TZD started	1702 (20.3%)	1103 (18.6%)
Statin dose increased	418 (5%)	268 (4.5%)
No statin therapy change	**6249 (74.7%)**	**4561 (76.9%)**
No statin prescription	3606 (43.1%)	2641 (44.5%)
Statin dose not increased	2643 (31.6%)	1920 (32.4%)

Conclusion: While the data from clinical trials suggest that rosiglitazone is associated with larger increases in LDL-C than pioglitazone, concomitant usage of statins by DoD patients is very similar for both drugs. The Council voted 8-2 to expand the authorized procurement strategies for the TZD class to include a closed class contract that does not mandate that patients be switched from a non-contracted TZD to a contracted TZD.

D. *Status of contracting initiative for statins* – The Council reviewed recent label changes for simvastatin (Zocor) that Merck voluntarily initiated with the FDA as a result of normal post-marketing surveillance and monitoring of ongoing clinical trials. The label changes approved by the FDA on 6 June 2002 further clarify the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin and when used with other drugs. Myopathy and rhabdomyolysis are well-known side effects of all statins. The revised label includes the following:

- *Concomitant use with fibrates and niacin (≥1g/day)* – simvastatin dose should not exceed 10 mg daily unless the benefit outweighs the increased risk.
- *Concomitant use with amiodarone or verapamil* – simvastatin dose should not exceed 20 mg daily unless the benefit outweighs the increased risk. In a clinical trial, 6% of patients taking amiodarone and simvastatin 80 mg daily developed myopathy. Combined clinical trial data showed a 0.6% risk of myopathy with simvastatin (20-80 mg) and verapamil.
- *Dose-related risk of myopathy/rhabdomyolysis* – the incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg & 0.3% at 80 mg.

The Council noted that a recent Clinical Advisory on the Use and Safety of Statins from the National Heart, Lung, and Blood Institute, the American College of Cardiology, and the American Heart Association states that a review of data regarding reports of fatal rhabdomyolysis among the different statins strongly suggests that there are no clinically important differences in the rate of

fatal complications among the five statins now available in the U.S., and that clinicians should consider the rates of severe myopathy as equivalent among these statins.

The Council unanimously concluded that the simvastatin label change is not cause to alter its previous decision to support any contracting/formulary strategy (to include a closed class contract) that places at least one high potency statin on the BCF and does not require patients to be switched from one agent to another.

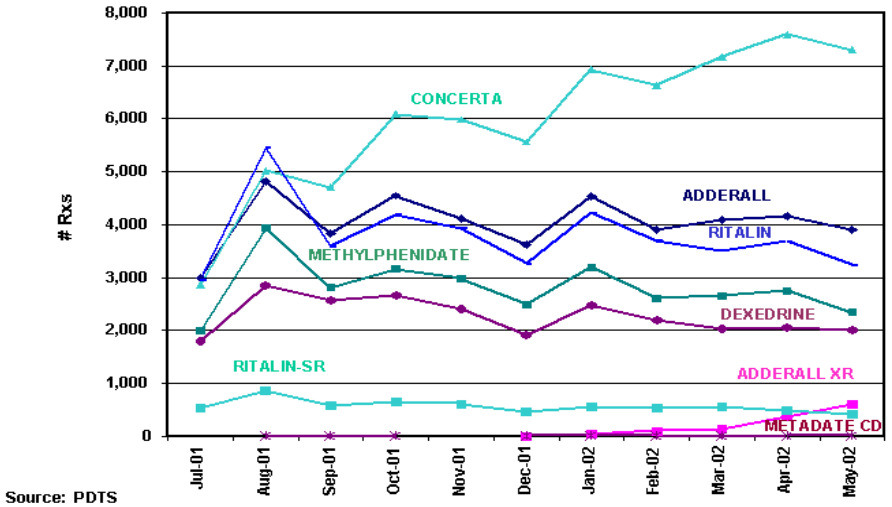
8. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES:

A. *Attention Deficit Hyperactivity Disorder (ADHD) stimulant medications* — Based on a recommendation from the PEC, the Council reviewed the list of stimulant medications currently included on the BCF for the treatment of ADHD. The stimulants most widely used for ADHD treatment are methylphenidate, dextroamphetamine, and mixed salts of amphetamine/dextroamphetamine. Methylphenidate is available in immediate-release, sustained-release, and extended release forms. Dextroamphetamine is available in immediate and extended release forms, while the mixed salts of amphetamine/dextroamphetamine are available in sustained release (Adderall and generics) and extended release (Adderall XR) forms. The three agents currently on the BCF are all methylphenidate products: methylphenidate immediate release, methylphenidate sustained release, and Concerta. Pemoline is another stimulant medication used for ADHD, but its side effect profile is not acceptable to most clinicians. Pemoline is reserved as a last-line therapy when all other treatments have failed, and was not considered further in this review.

Therapeutic interchangeability/clinical coverage: There appear to be two subsets of ADHD patients: those who respond to methylphenidate and those who respond to amphetamine products. According to the literature, initial treatment of ADHD with a stimulant medication from a particular class has approximately a 65% likelihood of success. A substantial number of treatment failures can be successfully treated with the alternate drug class. Which class is used first is largely a matter of prescriber preference, as there are no clinical features that predict which class of drugs is more likely to be successful for a given patient. Given these facts, a health system should have products and dosage forms from both the methylphenidate and amphetamine classes available to meet the clinical needs of its ADHD patients. Once a class of drugs is found to be effective, current practice guidelines for the treatment of ADHD recommend that patients be changed to an extended release formulation to enhance compliance, decrease the risk of drug diversion within the school setting, and minimize the stigma associated with school-age children taking midday doses of stimulants. Therefore, optimal management of ADHD requires the availability of both methylphenidate and amphetamine products, and requires that preference be given to dosage forms that minimize the likelihood that patients will need to take additional doses of medication during the school day.

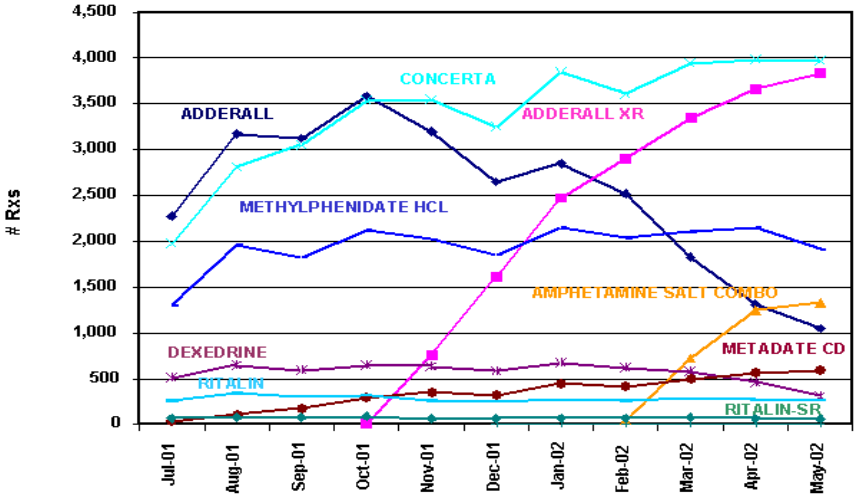
Utilization: The utilization trends within the MTFs and retail network pharmacies are presented in Figures 1 and 2.

Figure 1: MTF Prescriptions for ADHD Stimulant Medications (Jul 01 – May 02)



Source: PDTS

Figure 2: Retail Network Prescriptions for ADHD Stimulant Medications (Jul 01 – May 02)



Source: PDTS

Concerta is the most commonly dispensed stimulant medication at MTFs, with Adderall currently in second place. This is in sharp contrast to the retail network, where Concerta is also the most commonly dispensed drug, but Adderall XR is in second place and rapidly gaining ground. It is also noteworthy that use of Ritalin SR is very low in both points of service, despite its current position on the BCF. The retail network utilization trends (where all products are uniformly available) support the contention that methylphenidate and amphetamine products should both be available for the provision of comprehensive care to patients with ADHD, and also show that providers preferentially select the extended release formulation of these products for long-term therapy.

Provider acceptance: There was strong support among DoD providers who treat children with ADHD for a more robust BCF with broadened clinical coverage for ADHD patients. More than half of the respondents felt that an amphetamine product (Adderall or Adderall XR) should be added to the BCF to improve clinical coverage. Providers indicated that they would not favor any procurement strategy that resulted in a closed class with a single entity or required patients to be switched from one drug class to another. Most physicians felt that parents would be very resistant to medication changes mandated by contract once their child was being effectively treated with a particular medication. All agreed that pemoline is not a candidate for the BCF due to its side effect profile.

Based on this review, the Council approved the following decisions:

- Retain Concerta and methylphenidate IR on the BCF.
- Remove methylphenidate SR from the BCF
- Add Adderall XR 10-, 20- and 30-mg strengths to the BCF. Facilities may add additional strengths if they desire, but they are not mandated to do so.

9. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Venlafaxine extended release capsules (Effexor XR)* – In February 2002 the Council reviewed the anxiolytic class and concluded that venlafaxine extended release (Effexor XR; Wyeth-Ayerst) was useful in the treatment of several anxiety disorders, particularly in patients with co-morbid depression. A decision to add venlafaxine extended release to the BCF was tabled at that time pending discussions with the company intended to increase the cost-effectiveness of this therapy. Consideration was deferred again in May, as discussions with the company were still ongoing. Subsequently, the company presented a verbal offer of a $0.10 per tablet price reduction on the 150 mg tablet in return for BCF status.

Table 4: Current FSS pricing of Effexor/Effexor XR:

Drug	Strength	Price/tablet	Cost/30 days
Effexor	25 mg	$0.57	$34.20
	37.5 mg	$0.60	$35.76
	50 mg	$0.61	$36.84
	75 mg	$0.66	$39.30
	100 mg	$0.69	$41.52
Effexor XR	37.5 mg	$1.06	$31.80
	75 mg	$1.19	$35.70
	150 mg	$1.29	$38.70

Given the current rate of growth in utilization of venlafaxine extended release, the MHS would likely realize a cost avoidance of over $200,000 annually by accepting this offer. More savings are possible if BCF addition facilitates MTF recapture of venlafaxine extended release prescriptions from the retail network. The Council voted unanimously to add venlafaxine extended release 37.5, 75, and 150 mg tablets to the BCF, contingent on the signing of a BPA between Wyeth-Ayerst and DSCP establishing the $0.10 price reduction for the 150 mg tablet.

B. *Insulin glargine (Lantus)* – The Council considered a proposal to add insulin glargine (Lantus; Aventis Pharmaceuticals) to the BCF. Insulin glargine is a modified human insulin designed to act as a peakless basal insulin product with a 24-hour duration of action. It was approved by the FDA in April 2000 but was not launched until May 2001. The major advantage of insulin glargine is an approximately 10% lower incidence of symptomatic hypoglycemia, nocturnal

hypoglycemia, and severe hypoglycemia compared to NPH insulin. Initial studies suggested that the efficacy of insulin glargine in reducing HbA_{1c} levels was equivalent to that of NPH. Other brief trials demonstrated a significant decrease in the fasting plasma or whole blood glucose levels compared to NPH. Abstracts presented at the most recent American Diabetes Association meeting suggested that the enhanced safety profile of insulin glargine allows for a more aggressive approach to escalating insulin therapy in both Type 1 and Type 2 diabetics, and that this more aggressive approach in fact leads to a significant decrease in HbA_{1c} levels compared to traditional therapy with NPH insulin.

Even though insulin glargine costs much more than human NPH insulin at MTF pharmacies ($25.38 versus $4.49 per 10 ml vial) and is currently on fewer than half of MTF formularies, the prescription volume for insulin glargine increased 3.5 fold at MTF pharmacies between October 2001 and May 2002. Prescription volume for insulin glargine increased 2.5 fold in the retail network during the same period.

The Council concluded that insulin glargine represents a true advance in the treatment of both Type 1 and Type 2 diabetes and that it should be uniformly available at MTF pharmacies. The Council voted unanimously to add insulin glargine to the BCF.

C. *Gabapentin (Neurontin)* – In February 2002 the Council reviewed gabapentin for potential addition to the BCF, due to high usage rate and high expenditures in the retail network. The Council decided not to add gabapentin at that time due to concern that gabapentin was not FDA approved for pain control and that it may pose a large cost burden to small MTFs. The FDA recently approved gabapentin for treatment of post herpetic neuralgia. A generic version of gabapentin may become available in the near future. In the retail network gabapentin is in the top 20 for expenditures and top 50 for number of prescriptions. Gabapentin is among the top 100 drugs for number of prescriptions in the MTFs and is on 70% of MTF formularies. Gabapentin usage has continued to rise in all three points of service, with the majority of use for neuropathic pain in the over-65 aged population. The Council voted unanimously to add gabapentin to the BCF.

10. CLARIFICATION OF STATUS OF BLOOD GLUCOSE TEST STRIPS ON BCF – Precision (Abbott) blood glucose test strips have been on the BCF since its inception. Precision's status on the BCF is supported by an incentive price agreement that offers a lower price system-wide as market share increases. A medical/surgical product standardization initiative for TRICARE Regions 6, 7 and 8 recently selected the Accucheck (Roche Diagnostics) blood glucose test strip. Some pharmacies were incorrectly told that they had to switch from Precision test strip to the Accucheck test strip. LCDR Briski wrote an article in the May edition of the *PEC Update* and also disseminated information through the service pharmacy consultants/specialty leaders to MTF pharmacies to clarify that Precision test strips remain on the BCF and that regional medical/surgical standardization initiatives do not create "sole source" agreements that force MTFs to switch away from an item listed on the BCF.

The Army serves as the Executive Agent for medical/surgical regional standardization. The Council agreed that COL Remund should meet with COL Kissane, the Army OTSG/MEDCOM Deputy Chief of Staff for Logistics, to work out some rules of engagement that would enable national standardization through the BCF and regional standardization initiatives to productively coexist.

LCDR Briski also briefed the Council about Abbott Diagnostic's plan to phase out the Precision QID strip and meter, while phasing in their newer product, Precision Extra. The Precision Extra

product offers significant advancements over the Precision QID product. The Council voted to reaffirm its intent to keep Precision products as the sole blood glucose strip on the BCF. The Council encourages MTFs to expeditiously transition to the Precision Extra product.

11. CLARIFICATION OF 27- AND 54-MG STRENGTHS OF METHYLPHENIDATE EXTENDED RELEASE (CONCERTA) – When Concerta was first added to the BCF in November 2000, the only strengths available were 18 mg and 36 mg. A 54 mg capsule was marketed in December 2000, and a 27 mg capsule was added in April 2002. Multiple strengths allow more precise titration of dosages. During a recent PEC review of Concerta utilization at MTFs, it was noted that several large MTFs were dispensing a large number of dual prescriptions to patients for both 18 mg and 36 mg Concerta capsules rather than for 54 mg capsules. This results in an inconvenience to the patient, an increase in workload for the pharmacy, and an excess cost of $38.40 per patient per month.

To facilitate dosage titration and to maximize the likelihood that Concerta will be used in as cost-effective a manner as possible, the Council voted to add the 27 mg and 54 mg strengths of Concerta to the BCF. The vote was 8 in favor, one against, and one abstention.

12. MTF REQUESTS FOR BCF CHANGES

A. Requests to delete particular strengths or dosage forms of BCF items – The Health Affairs Policy for Basic Core Formulary and Committed Use Requirements Contracts (Policy #98-034) states, "In the case of multiple strength BCF drugs, all strengths need not be stocked but all prescriptions for that agent will be filled regardless of strength." The BCF page on the PEC website explains that a listing for an oral medication "indicates all oral dosage forms and strengths will be provided unless otherwise noted." The DoD P&T Executive Council has deleted or excluded some dosage forms/strengths from the BCF for one or more of the following reasons:

- Substantially higher cost than other dosage forms/strengths
- Excessive administrative burden associated with maintaining multiple strengths (e.g., controlled substances)
- The BCF listing is intended to cover an indication that is limited to a specific dosage form/strength (e.g., fluconazole 150 mg for vaginal yeast infections)
- New dosage form/strength offers no significant clinical advantage and is apparently designed to avert competition from generic versions of the drug
- Low usage combined with one or more of the factors above

Some MTF requests to delete a particular strength or dosage form of a BCF drug appear to be based primarily on objections to stocking an item that has a low usage rate. The Council reiterates that if an MTF has little or no demand for a particular BCF item, the MTF is not required to physically stock the item in the pharmacy. However, the MTF must provide the item if it is prescribed.

B. *Request to remove cimetidine from the BCF* – A MTF pharmacist requested the deletion of cimetidine from the BCF due to low usage. Cimetidine and ranitidine are the two H2 blockers currently on the BCF. Ranitidine prescriptions outnumber cimetidine prescriptions 9 to 1 at MTF pharmacies. Indications and efficacy are similar for both drugs, but cimetidine has more side effects and drug interactions than ranitidine. Ranitidine costs $0.06 - $0.07 per day; cimetidine costs $0.10 to $0.13 per day. The Council voted unanimously to delete cimetidine from the BCF. MTFs may decide to retain cimetidine on their local formularies if so desired.

C. *Request to remove cyproheptadine from the BCF* –An MTF pharmacist requested deletion of cyproheptadine from the BCF because there are better alternatives on the BCF to treat allergies and headache and because cyproheptadine had been dispensed fewer than 20 times in the past 6 months at the requestor's MTF. More than 90 responses were received from providers and pharmacists in the field, overwhelmingly and convincingly offering reasons why this drug should be maintained on the BCF in spite of low usage. Cyproheptadine has a unique place in therapy with no good alternative treatments for pregnant patients and young children with migraine headaches, in addition to other uses. The 4 mg tablet is priced as low as $0.03 per tablet, and the 2 mg per 5 ml syrup costs $0.15 per 5 ml. The Council voted unanimously to retain cyproheptadine on the BCF.

D. *Request to remove theophylline elixir from the BCF* –An MTF pharmacist requested deletion of theophylline oral liquid from the BCF because it has been dispensed less than 20 times in the past 6 months at the requestor's MTF. Children and elderly patients who cannot swallow solid dosage forms or are unable to use a metered-dose-inhaler effectively account for almost all of the theophylline oral liquid use. Theophylline remains on asthma and COPD treatment guidelines, and the oral liquid form is the only dosage form that is suitable for some patients. Theophylline oral liquid is inexpensive ($0.003 to $0.045 per ml). The Council voted unanimously to retain theophylline oral liquid on the BCF.

E. *Request to add budesonide inhalation suspension (Pulmicort Respules) to the BCF* – A pediatrician requested addition of budesonide inhalation suspension to the BCF for the following reasons: 1) it is the only FDA-approved, nebulized steroid available and can be used for patients as young as 12 months of age; 2) prior to the availability of budesonide inhalation suspension, steroid metered dose inhalers (MDIs) were used for persistent asthmatics—young children could not always cooperate effectively with these; 3) parents appreciate the convenience of nebulized medications in children and studies have shown them to be efficacious; and 4) one in nine children has asthma—addition would enhance primary care options for treatment.

   The safety and tolerability of nebulized budesonide are no different than other inhaled steroids. Both inpatient and outpatient studies have shown efficacy in respect to symptom relief. As expected, use of this medication is low and almost exclusively for patients in the 0 to 4 age group, which is consistent with appropriate use of the product. MDIs are still the inhaled steroid formulation of choice in the treatment of asthma. Budesonide inhalation suspension is intended for those who cannot yet use MDIs appropriately. The Council voted unanimously to add budesonide inhalation suspension (Pulmicort Respules) to the BCF.

F. *Request to add meloxicam (Mobic) to the BCF* – The PEC received two requests to add meloxicam to the BCF, one from an Air Force physician and one from an Army pharmacist. Both requestors represent facilities currently using meloxicam as an alternative to "COX-2 inhibitors" (rofecoxib, celecoxib, or valdecoxib).

The Council considered the following points:

- *Background* - Meloxicam is FDA-approved only for osteoarthritis (OA). Because patent protection/exclusivity for meloxicam is expected to expire within the next three years, the manufacturer has stated that they do not plan to pursue additional indications. The drug is approved in various European countries for rheumatoid arthritis (RA). Despite its relatively recent introduction in the U.S. in April 2000, meloxicam has been available in other countries since 1995. The manufacturer estimates that more than 45 million patients have been exposed to meloxicam worldwide.
- *Efficacy* - There are published clinical trials showing efficacy of meloxicam for the treatment of OA, RA, and other chronic painful conditions, including ankylosing spondylitis and low back pain. Publication of the IMPROVE trial, a 6-month naturalistic (effectiveness) trial in OA patients (meloxicam vs. "usual care" NSAIDs) is expected shortly; summary results are available in abstract.
- *Safety –NSAID-associated GI adverse events*
  - *COX-2 selectivity* - The most extensive analysis of COX-2/COX-1 selectivity of NSAIDs to date (Warner et al. Proc Nat Acad Sci 1999; 96:7563-8) constructed the following ranking based on a whole blood assay (from most COX-2 selective to least COX-2 selective): rofecoxib (>50-fold COX-2 selective); etodolac, meloxicam, and celecoxib (grouped together as 5-to 50-fold COX-2 selective); diclofenac, sulindac, piroxicam, ibuprofen, tolmetin, naproxen, aspirin, indomethacin, ketoprofen, ketorolac. According to other researchers, the COX-2 selectivity of meloxicam appears to be dose-related, with greater COX-2 selectivity at a daily dose of 7.5 mg than at 15 mg.
  - *Association of COX-2 selectivity with reduced incidence of serious upper GI events* - The major potential advantage of COX-2 selective NSAIDs relative to non-selective NSAIDs is a reduction in the incidence of complicated upper GI events (GI bleed, perforation, and obstruction) and symptomatic but uncomplicated ulcers. Evidence of a reduced incidence of complicated upper GI events compared to nonselective NSAIDs is most conclusive with rofecoxib, less conclusive with celecoxib and meloxicam, and not yet available for valdecoxib. Because no head-to-head trials of sufficient size and duration to discern a clinically significant difference in complicated upper GI events are available, it is difficult to compare the incidence rate of complicated upper GI events with meloxicam and celecoxib, rofecoxib, or valdecoxib. See Appendix A for a discussion of clinical studies involving meloxicam, celecoxib, and rofecoxib.
- *Safety: Cardiorenal and cardiovascular adverse events* - NSAIDs, including celecoxib, rofecoxib, and valdecoxib, are known to cause fluid retention, edema, blood pressure (BP) elevation, and loss of BP control in patients treated with antihypertensive medications. In addition, the VIGOR trial with rofecoxib showed a statistically significantly higher incidence of adjudicated serious cardiovascular thrombotic events (primarily acute myocardial infarctions) in patients treated with rofecoxib 50 mg QD compared to patients treated with naproxen 500 mg BID [1.1% vs. 0.5%, NNH=167].

Pooled data from the Meloxicam Serious GI Event Analysis, which includes clinical trial data involving 27,039 patients who received meloxicam, comparator NSAIDs, or placebo in 35 clinical trials, provides comparative information on the incidence of these adverse events in patients treated with meloxicam or comparator NSAIDs (see Table 5). Placebo data included in this analysis are very limited (736 patients, 113 patient-years of therapy) and are not included in the table because they are unlikely to accurately reflect background rates.

Table 5: Rates of cardiovascular/cardiorenal adverse events

	Meloxicam	NSAIDs
Patients	15,071	11,078
Patient-years of therapy	3129	1202
Myocardial Infarctions (incidence/100 pt-yrs)	18 (0.58%)	8 (0.67%)
Cardiac Failure (incidence/100 pt-yrs)	15 (0.48%)	7 (0.58%)
Peripheral Edema (incidence/100 pt-yrs)	98 (3.13%)	79 (6.57%)
Hypertension (incidence/100 pt-yrs)	82 (2.62%)	32 (2.66%)
Aggravated HTN (incidence/100 pt-yrs)	25 (0.80%)	15 (1.25%)

- *Tolerability* - Meloxicam appears to be as well or better tolerated than the NSAIDs to which it was compared in clinical trials. In the MELISSA study, fewer patients treated with meloxicam withdrew from the study due to GI adverse effects (e.g., dyspepsia, nausea, abdominal pain) compared with diclofenac (3.0% vs. 6.1%); similar results were observed in the SELECT trial (3.8% vs. 5.3% with piroxicam). Preliminary results from the IMPROVE study show significantly fewer discontinuations of therapy due to adverse effects compared to "usual care" NSAIDs.
- *Other Factors*
  - *Frequency of Dosing* - Meloxicam is dosed once daily.
  - *Provider Input* - The PEC requested provider (physician and pharmacist) input on this issue. Because the VA has selected etodolac for their COX-2 criteria as an alternative to salsalate for patients at significant GI risk, and because etodolac, like meloxicam, has at least some evidence of a lower incidence of GI adverse events than other NSAIDs, providers were asked about etodolac as well as meloxicam. Providers were asked: 1) if their MTF would use meloxicam or etodolac if added to the BCF, 2) the place of the drug(s) in therapy, 3) should meloxicam or etodolac be added to the BCF, and 4) how addition would affect their facility. The responses were mixed. Key points included:
    - One responder pointed out that while BCF addition would probably have a significant budgetary impact on facilities that currently have no COX-2s on formulary, the overall cost to DoD should drop significantly if these facilities would call civilian providers and switch COX-2 prescriptions to meloxicam, preventing a significant number of COX-2 prescriptions from being filled in the network at a higher overall cost to DoD. MTFs that currently do not have COX-2 inhibitors on formulary may incur increased costs.
    - Some responders were concerned that if meloxicam were added to formularies without restrictions, providers may shift from prescribing lower cost generic NSAIDs to prescribing meloxicam, even in patients at low risk for GI adverse events.

  - Some responders doubted that providers would use meloxicam or etodolac in place of rofecoxib or commented that these are low use items at their facilities.
  - Some responders commented that there was insufficient clinical trial evidence to conclude that meloxicam is COX-2 sparing.
  - With regard to etodolac, responders commented that while it is generically available and less costly than meloxicam and there is some evidence that it is COX-2 sparing; it must be dosed 2-3 times per day and is not actively marketed to providers. Comments about the effectiveness of etodolac ranged from "good success" to "useless" (and must, in any case, be regarded as anecdotal).

- *Status on MTF formularies* - Facilities that currently have meloxicam on formulary (either unrestricted or as part of a step therapy program that requires failure of one or more nonselective NSAIDs prior to meloxicam) include: Tripler Army Regional Medical Center (ARMC); Madigan ARMC; Brooke Army Medical Center, Wilford Hall Medical Center, Randolph Air Force Base (AFB); Ft. Polk; Luke AFB; Ft. Hood; Ft. Leonard Wood; William Beaumont ARMC; and Nellis AFB.
- *Dose distribution - MTFs vs. retail network* - Since the COX-2 selectivity of meloxicam appears to be dose-related, the percentage of patients receiving 7.5- vs. 15-mg daily doses is of interest. As of July 2002, about 80% of meloxicam prescriptions filled in the NMOP and retail network were for the 7.5-mg strength of meloxicam, which is consistent with the 80-85% reported by the manufacturer as typical in the civilian marketplace. Only about 35% of meloxicam prescriptions filled at MTFs were for the 7.5 mg strength; however, the true percentage of MTF meloxicam prescriptions written for a 7.5-mg daily dose is likely to be closer to 65% due to splitting of the 15-mg tablet (see following analysis).
- *Cost*
  - *Dose distribution and MTF cost per day* - The PEC analyzed signatura (directions for use) for all MTF prescriptions for meloxicam, celecoxib, rofecoxib, and etodolac with valid signatura in the Uniformed Services Prescription Database from Jan – April 2002 (134,883 Rxs). This analysis served two purposes: to analyze the dose distribution of meloxicam and to compare the weighted average cost per day of meloxicam to the COX-2 inhibitors and to etodolac. Valdecoxib was not included due to the limited number of MTF prescriptions during this time period.

Table 6: Dose distribution and weighted average daily cost

Generic	Strength / dosage form	Daily dose (# tabs/caps per day)	% of Rxs	Average cost per tab/cap purchased by MTFs	Weighted average daily cost
Meloxicam	15 mg tab	0.5 1	39.6% 34.6%	$0.97	$0.80*
	7.5 mg tab	1 2	19.5% 5.9%	$0.88	
Celecoxib	100 mg cap	1 2	5.9% 15.8%	$0.80	$1.76
	200 mg cap	1 2	54.2% 23.2%	$1.45	
Rofecoxib	12.5 mg tab	1	7.6%	$1.35	$1.43
	25 mg tab	1 2	71.5% 5.9%	$1.37	
	50 mg tab	0.5 1	6.5% 5.7%	$2.13	
Etodolac	200 mg cap	2	2.0%	$0.15	$0.52
	300 mg cap	2 3	8.4% 2.3%	$0.20	
	400 mg tab	1 2 3 4	2.6% 70.4% 6.8% 2.2%	$0.27	

Based on all prescriptions with valid signatura (directions for use) in the Uniformed Services Prescription Database Jan – April 2002 and the average price per tab/cap purchased by MTFs, based on prime vendor data for Apr – May 02. Rows representing less than 2% of all prescriptions for a specific medication are omitted; percentages may not add to 100% for this reason. Usage of extended release etodolac was extremely low and is not reflected in these results.
* Results for meloxicam reflect a high percentage of prescriptions for meloxicam 15 mg tabs as 0.5 tabs per day, most likely due to tablet-splitting. In the absence of tablet-splitting strategies (i.e., substitution of 7.5 tabs for all 15 mg half-tabs), the weighted average cost per day would be about $0.96.

- The manufacturer has offered DoD a blanket purchase agreement for meloxicam. The BPA provides a price reduction from $0.89 to $0.79 for the 7.5 mg tab and from $0.98 to $0.88 for the 15 mg tab, a reduction of about 11%, in return for placing meloxicam on the BCF. The BPA would be effective no later than Oct 2002 and run through 31 Dec 2003. The BPA does not prevent later addition of a COX-2 inhibitor or any other NSAID to the BCF. Using the same method described above, these price decreases would reduce the weighted average daily cost of meloxicam from $0.80 to $0.73 per day.

The Council agreed that the evidence for a GI-sparing effect with meloxicam is not as certain as that for rofecoxib, but that there is sufficient evidence to conclude that meloxicam is associated with fewer serious GI events than the less COX-2 selective NSAIDs with which it has been compared in clinical trials. The Council emphasized that because meloxicam is still substantially more costly than generic NSAIDs (e.g., naproxen, ibuprofen, diclofenac), it does not make sense to use meloxicam in patients at low risk of GI events.

It is difficult to accurately predict whether addition of meloxicam to the BCF will result in greater cost (if meloxicam is used in place of generic NSAIDs) or cost avoidance (if meloxicam is used in place of celecoxib, rofecoxib, or valdecoxib). One large Army MTF that previously had celecoxib and rofecoxib on formulary with a criteria-based prospective medication use evaluation form deleted celecoxib and rofecoxib from their formulary and added meloxicam after discovering that a majority of the patients receiving celecoxib or rofecoxib did not meet criteria. After 4 months, they reported substantial cost avoidance, no adverse drug reactions, no new drug requests for celecoxib or rofecoxib as a result of treatment failures, and a 100% conversion rate when outside providers were contacted requesting a change to meloxicam.

The Council voted to add meloxicam (Mobic) to the BCF. The Council agreed that facility-level guidelines or programs to ensure appropriate use of meloxicam, as well as celecoxib, rofecoxib, or valdecoxib, are consistent with BCF policy as long as the guidelines are applied uniformly and consistently (e.g., to both military and civilian providers).

The Council also considered addition of etodolac to the BCF, but decided that it did not have sufficient data concerning the clinical utility and GI-sparing effect of etodolac and tabled the issue to a later date.

G. *Request to add aspirin/extended release dipyridamole (Aggrenox) to the BCF* – Two providers, a neurologist and a neuro-ophthalmologist, requested that Aggrenox (aspirin 50 mg/extended release dipyridamole 200 mg) be added to the BCF. Aggrenox is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. Aggrenox does not have approval for coronary heart disease. The 1999 AHA guidelines for the Management of TIA identify Aggrenox as an acceptable option for initial therapy following a TIA, along with aspirin, clopidogrel and ticlopidine. All have been shown to reduce the risk of recurrent stroke in patients who have had a TIA. Clopidogrel is indicated for reduction of thrombotic events in patients with recent stroke or established peripheral arterial disease, and is also indicated for use in unstable angina or myocardial infarction. Clopidogrel was added to the BCF in February 2002

Safety and tolerability of Aggrenox are similar to the two separate ingredients used in combination, with headache as the major limitation. The European Stroke Prevention Study-2 (ESPS-2) was the major efficacy trial for Aggrenox. Dropout rates in the Aggrenox and dipyridamole groups of the ESPS-2 were significantly higher than those reported in the aspirin and placebo groups. The high overall dropout rate (26%) raises the question of poor patient compliance.

There is no conclusive evidence that Aggrenox offers a significant advantage over the concomitant use of aspirin and dipyridamole to reduce the risk of stroke. The relative risk reduction for aspirin and dipyridamole versus placebo in the ESPS-1 study (38.1%) was similar to the relative risk reduction for Aggrenox versus placebo in the ESPS-2 study (37.2%).

Aggrenox is significantly more expensive than using separate tablets of aspirin or dipyridamole together. Aggrenox costs $1.76/day, which is similar to clopidogrel at $1.80/day. PDTS usage data from July 2001 – June 2002 showed there were only 2000 Aggrenox prescriptions vs. 20,000 clopidogrel prescriptions in the entire DoD.

Only 25 responses were obtained from providers regarding potential BCF addition of Aggrenox, of whom 20 were against BCF addition. Aggrenox has minimal usage in DoD, is not supported by the primary care providers, and does not offer clear benefit over clopidogrel. The Council voted not to add Aggrenox to the BCF. Individual MTFs may add Aggrenox to their local formulary if desired.

13. ADJOURNMENT

The meeting adjourned at 1430 hours on 7 August 2002. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland starting at 0800 on Wednesday, 20 November 2002. All agenda items should be submitted to the co-chairs no later than 18 October 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Appendix A: Studies Indicating a Reduced Incidence of Complicated Upper GI Events with Rofecoxib, Celecoxib, or Meloxicam

Abbreviations used in this appendix: absolute risk reduction (ARR); confidence intervals (CI); relative risk (RR), number-needed-to-treat (NNT); number-needed-to-harm (NNH)

Rofecoxib

- The VIGOR trial (Bombardier et al. N Engl J Med 2000; 343:1520-8) compared rofecoxib and naproxen in 8000+ RA & OA patients. The median duration of the trial was 9 months; patients on aspirin were excluded. This trial provides the best evidence to date that a COX-2 selective NSAID results in fewer complicated upper GI events (perforations, obstructions, or upper GI bleeds) and symptomatic ulcers. The incidence of confirmed complicated upper GI events was 0.6% in the rofecoxib group vs. 1.4% with naproxen [absolute risk reduction (ARR) = 0.8%, relative risk (RR) = 0.43 (95% CI 0.24-0.78), p=0.005, number needed to treat (NNT) = 125], while the incidence of the combined endpoint of confirmed complicated upper GI events **or** symptomatic ulcers was 2.1% with rofecoxib vs. 4.5% with naproxen [ARR=2.4%, RR=0.46 (95% CI 0.33-0.64), p<0.001, NNT=41].

Celecoxib

- The CLASS trial (Silverstein et al. JAMA 2000; 284:1247-55) compared celecoxib vs. a pooled NSAID group (ibuprofen or diclofenac) in 8000+ OA patients. The duration of the trial was approximately 13 months (6-month results published); patients on prophylactic aspirin were included. Published (6-month) data from the CLASS trial reported fewer confirmed complicated upper GI events with celecoxib vs. pooled NSAIDs, but the difference was not statistically significant [0.76% celecoxib vs. 1.45% NSAIDs; ARR 0.69%; RR=0.53 (95% CI 0.26-1.11), p=0.09]. A statistically significant difference was found for the combined endpoint of complicated upper GI events **or** symptomatic ulcers [2.08% celecoxib vs. 3.54% NSAIDs; ARR 1.46%; RR=0.59 (95% CI 0.38-0.94), p=0.02]. About 22% of patients were receiving low-dose aspirin. A subgroup analysis of patients not receiving aspirin resulted in significant results for celecoxib vs. pooled NSAIDs for both endpoints; there were no differences between celecoxib and pooled NSAIDs in patients receiving low-dose aspirin.

  Subsequent to initial publication, FDA briefing documents and reviews (available at www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm) were made available addressing the entire duration of the trial. When the entire 13-month study period was considered, there was no significant difference between celecoxib and the pooled NSAID group for the primary endpoint of confirmed complicated UGI events in the overall study population, the subgroup of patients not receiving aspirin, or the subgroup of patients receiving aspirin. The differences in statistical significance between six-month data and data from the entire study period appeared to be due to the occurrence of relatively more confirmed complicated UGI events in the celecoxib group than in NSAID groups subsequent to the first six months (see Table 7).

Table 7: Number of confirmed complicated UGI events in the CLASS trial
(uncensored intent-to-treat data)

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
First 6 months	11	9	11
Entire Study Period	17	10	11

Adapted from Tables 13 and 14, Medical Officer Review for Celebrex®, available at: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc

FDA briefing documents and reviews also provide separate data for the two comparator NSAIDs, which was not available in the published report. All differences that were statistically significant between celecoxib and the pooled NSAID group were significant for celecoxib versus ibuprofen. Regardless of aspirin use, there was no difference between diclofenac and celecoxib in any endpoint.

Meloxicam

- Two large (8000+ patient) meloxicam safety trials have been published, SELECT (Dequeker et al. Brit J Rheumatol 1998; 37:946-51) and MELISSA (Hawkey et al. Brit J Rheumatol 1998; 37:937-45). Each of the two 28-day trials randomized patients with OA to meloxicam or a comparator NSAID (piroxicam in SELECT and diclofenac in MELISSA); the trials were otherwise of identical design. The choice of NSAID comparators facilitated comparison of results with meloxicam vs. both a relatively COX-1 selective NSAID (piroxicam) and a relatively COX-2 selective NSAID (diclofenac). In SELECT, 7 patients treated with meloxicam had complicated upper GI events or ulcerations compared to 16 patients treated with piroxicam. All four cases involving perforations or bleeding occurred with piroxicam. In MELISSA, 5 patients treated with meloxicam had complicated upper GI events or ulcerations compared to 7 patients treated with diclofenac. Although both comparisons were statistically nonsignificant, the numerical results are consistent with the known COX-2 selectivity of the comparators.
- While meloxicam lacks a GI safety study comparable in size and duration to VIGOR or CLASS, summary results of large pooled analyses of clinical trial data are becoming available. Summary results of a pooled analysis of meloxicam clinical trial data involving 27,039 patients who received meloxicam, comparator NSAIDs, or placebo in 35 clinical trials have been published in abstract by Dr. Singh and colleagues, and are available from the manufacturer as the "Meloxicam Serious GI Event Analysis." (Note: multiple abstracts concerning this analysis are available at www.eular.org; search 2001 & 2002 abstracts for "meloxicam.")
- An analysis of complicated upper GI events (perforations, obstructions, or clinically serious upper GI bleeds) per 100 patient-years in patients who received placebo, various doses of meloxicam, diclofenac, or piroxicam during meloxicam clinical trials is shown in the table below (Singh G, Triadafilopoulos G. European Congress of Rheumatology, June 2001. Abstract SAT0085). The rate of complicated upper GI events with meloxicam appeared to be dose-related and lower than rates with diclofenac or piroxicam.

Table 8: Rate of complicated UGI events & NNH

Drug	N	Cumulative pt-yrs	Events	Events per 100 pt-yrs	NNH*
Placebo	736	113	0	0	-
Mel 7.5 mg	10158	918	3	0.3	333
Mel 15 mg	2960	1451	9	0.6	167
Mel 22.5	910	600	6	1.0	100
Diclofenac	5464	524	9	1.7	59
Piroxicam	5371	603	16	2.7	37

NNH = number-needed-to-harm to cause 1 additional event compared to placebo

- Preliminary results from an even larger pooled analysis are available in abstract (Furst et al, European League Against Rheumatism 2002, Stockholm, Sweden. Abstract THU0264, available online at www.eular.org). The analysis included data from 48 clinical trials including 117,755 patients with rheumatic diseases who received meloxicam, comparator NSAIDs, or placebo during meloxicam clinical trials. Cumulative hazards (95% CI) after 3 months for complicated upper GI events (perforations, obstructions, or GI bleeds) was: 0.05% (0-0.12%) for meloxicam 7.5 mg; 0.42% (0.12-0.71%) for meloxicam 15 mg; estimate for diclofenac 0.51% (0.16-0.86%); estimate for piroxicam 1.11% (0.35-1.88%).

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **8 MAY 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T Committee convened at 0800 hours on 8 May 2002, at the Commissioned Officers Club, Fort Sam Houston, TX

2. MEMBERS PRESENT

CDR Terrance Egland, MC, USN	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS, USA	DoD P& T Committee Co-chair
Col John R. Downs, MC	Air Force
Col Mark Nadeau, MC (For Col Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly	Army
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
William Hudson	Humana
Gene Lakey	TriWest
Ray Nan Berry	Health Net Federal Services
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)

MEMBERS ABSENT

COL Rosa Stith, MC	Army
Ron McDonald	Sierra Military Health Services

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
LTC Don DeGroff	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, USAF, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
Maj Barb Roach, USAF, MC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
HM1 Lisa Drumm	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
David Chicoine	Uniformed Services Family Health Plan
Mark Petruzzi	Merck-Medco
Elizabeth Scaturro	Merck-Medco Managed Care
David Spiler	Merck-Medco
CAPT Howard Hays	USPHS/Indian Health
CAPT Samuel Hope	USPHS/Indian Health
CAPT Robert Pittman	USPHS/Indian Health
LCDR Thomas Berry	USPHS/Indian Health

3. **REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **INTERIM DECISIONS** – COL Remund reported on interim decisions:

   - Interferon beta 1a (Rebif) was added to the NMOP covered injectables list because interferon beta 1a (Avonex) and interferon beta 1b (Betaseron) were already included on the list.
   - In response to safety concerns raised by the FDA, Roche Laboratories implemented the System to Manage Accutane Related Teratogenicity (SMART) program on 10 April 02. The SMART program includes prescribing restrictions that make it infeasible for the NMOP to continue to fill Accutane prescriptions, so Accutane was removed from the NMOP Formulary.

5. **UNIFORM FORMULARY (UF) PROPOSED RULE**- COL Davies presented an extensive description of the UF proposed rule. The UF Proposed Rule was posted on the following website: http://frwebgate.access.gpo.gov/cgi-bin/multidb.cgi; Federal Register, Vol 67, No 71, FRI 12 Apr 2002; Civilian Health and Medical Program of the Uniformed Services. The proposed rule will be open to public comment until 11 June 2002. Comments may be submitted by email to: uniformulary@tma.osd.mil.

6. **ACADEMY OF MANAGED CARE PHARMACY (AMCP) FORMAT FOR FORMULARY SUBMISSIONS** – The AMCP developed the Format for Formulary Submissions in order to (1) improve the timeliness, quality, scope, and relevance of information available to P&T committees, and (2) streamline the data acquisition and review process for managed care organization staff pharmacists. The Format requires pharmaceutical companies to construct "dossiers" that provide drug information in a standardized format. Each dossier contains the following sections: product information, supporting clinical and economic information, an impact model report (to predict system-wide consequences of formulary changes), clinical value and overall cost, supporting information. COL Remund reported that the PEC will ask pharmaceutical companies to submit dossiers on new agents. Use of the AMCP Format will hopefully reduce the burden on the PEC staff for compiling drug information and allow more time for analyzing the information.

7. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 7 new drugs or formulations (see Appendix A).

8. **REEVALUATION OF SILDENAFIL (VIAGRA) POLICY** – Tabled until the meeting in August 02.

9. **NMOP AND RETAIL NETWORK ISSUES**

   A. Clarification of the "line extension rule" for the NMOP Formulary – Shana Trice (PEC) reported on the current process for determining the formulary status of new formulations and dosage forms of medications that are already on the NMOP Formulary. Non-injectable medications in the following categories are added to the NMOP Formulary without formal action by the DoD P&T Committee unless the NMOP contractor and the NMOP Contracting Officer's Technical Representative (COTR) identify a reason for the P&T Committee to be involved in the decision:

   a. Generic equivalent of an agent already on the NMOP formulary
   b. New dosage form of an agent already on the NMOP formulary
   c. New formulation of an agent already on the NMOP formulary
   d. New drug entity in a therapeutic class/category for which the Committee has previously approved automatic inclusion for new drug entities. Currently the only drug class to which this applies is AIDS/HIV drugs. The Committee will review drugs automatically included under this provision at the next scheduled meeting.

   New combination products of non-injectable medications that are already on the NMOP Formulary are added to the NMOP Formulary only upon the decision of the P&T Committee or by the co-chairs through the interim decision mechanism. This does not apply to therapeutic classes/categories in which the Committee has previously approved automatic inclusion for new drug entities (i.e., AIDS/HIV drugs).

   The Committee agreed that the current process is working and should be retained, but emphasized that the preceding categories should be applied as guidelines rather than absolute rules. If Merck-Medco personnel and the NMOP COTR agree that further review is warranted for any reason, the issue should be referred to the PEC for further investigation and a recommendation for the co-chairs and/or the Committee.

The Committee agreed that the same guidelines could be applied to addition of injectable medications to the NMOP Covered Injectables List, since Merck-Medco personnel and the NMOP COTR will look at new dosage forms, formulations, and combination products and will refer issues to the PEC for further review as needed.

B. Clarification of the NMOP quantity limits for antibiotics – Subsequent to a patient question regarding a quantity limit on an antibiotic prescription filled through the NMOP, Lt Col Zastawny presented information regarding quantity limits on antibiotics through the NMOP.

A general 30-day quantity limit on antibiotics from the NMOP and a list of antibiotics exempted from the 30-day quantity limit rule were approved by the Committee at the July 1998 meeting (http://www.pec.ha.osd.mil/PTC/ptmin078.pdf), and posted with the July 1998 P&T minutes. This information was never published on the PEC website's quantity limit page, so most committee members, providers, and patients are unaware of the 30-day quantity limit on antibiotics or the antibiotics that were exempt from the 30-day limit. The NMOP contractor, however, has applied the 30-day quantity limit to antibiotic prescriptions filled through the NMOP. According to the NMOP COTR, antibiotic quantity limits in the NMOP have caused very few complaints over the past 3 years.

The Committee decided to table this topic until the August 2002 meeting in order to allow members time to review the antibiotic quantity limits and make informed decisions.

10. PRIOR AUTHORIZATIONS (PAs)

A. Report on PA drugs – Shana Trice (PEC) reported that all changes to NMOP PA criteria approved at the last meeting had been completed and that PA forms, criteria, and clinical rationale explanations were posted on the PEC website.

B. Proposed revision to anakinra PA criteria – Given the current shortage of etanercept, the Committee discussed revising the anakinra PA criteria to make it easier for patients unable to obtain etanercept to be started on anakinra. They decided to make no changes because it does not appear that existing etanercept patients have been unable to receive etanercept for continuation of therapy (although the NMOP reported delays of some days in supplying etanercept to patients) and because making the administrative change to NMOP PA criteria would require at least 90 days.

C. Cost avoidance from NMOP PAs – The Committee approved the recommendation to report cost avoidance of NMOP PAs at every other meeting. The next report will be at the August 02 meeting.

11. SUBCOMMITTEE REPORT: PROVISION OF INJECTABLE DRUGS IN THE NMOP OR RETAIL NETWORK PHARMACIES – Lt Col George Jones reported that the subcommittee was uncertain about what it was supposed to do. The subsequent discussion focused on the possibility of applying the NMOP Covered Injectables List to the retail network to define what injectable products would be available from retail network pharmacies. COL Davies pointed out that the DoD P&T Committee does not have the authority to make such a decision, as this would constitute a change in the pharmacy benefit by making a group of drugs unavailable in both purchased care venues. Another committee member again stated the opinion that this was a safety issue, but the Committee felt that in general this was not the case. The Committee decided to disband the subcommittee.

The Committee subsequently considered that there may be injectable drugs being dispensed in the retail network that are not being dispensed through the NMOP that in fact could be provided through the NMOP. The PEC will use prescription data from PDTS to analyze this issue. Mr. Bill Hudson from Humana Health Care, one of the members of the original subcommittee, also expressed an interest in remaining involved with this issue. The Committee agreed with this course of action.

12. CONTROLLED DISTRIBUTION OF PRESCRIPTION DRUGS – The FDA has mandated controlled or restricted distribution mechanisms for several agents. The current status of those agents within the DoD is:

A. Schering, the manufacturer of pegylated interferon (PEG-Intron), emplaced a mechanism to allow DoD activities to order directly. Details will be available on the PEC website.

B. Pfizer, the manufacturer of dofetilide (Tikosyn), emplaced a mechanism to allow DoD activities to order directly, and the Managed Care Support Contractors are providing the drug through their retail pharmacy networks. Details will be available on the PEC website.

C. Members of the DoD Pharmacy Board of Directors are working with Roche and the FDA to establish a mechanism for Accutane to be prescribed via electronic physician order entry instead of requiring hard copy prescriptions.

D. Etanercept (Enbrel) is in short supply. Current patients' needs are being met. New patients are being placed on a waiting list. Relief is not expected soon. Providers are being advised to consider alternative therapy.

E. Actelion, the manufacture of bosentan (Tracleer), maintains five specialty distributors to distribute Tracleer. CVS Procare is one of the specialty distributors, and is part of the TRICARE retail network. All Tracleer patients should enroll into the Tracleer Access Program (TAP) by using the toll-free telephone number 866-228-3546. At that time they will be assigned to CVS Procare as their specialty pharmacy. None of the other specialty pharmacies are part of the MCSC retail pharmacy networks. Using any pharmacy other than CVS Procare would result in an out-of-network claim, which requires advance payment for the drug and the filing of a paper claim; the patient would only be reimbursed the cost of the drug minus a cost share, which is substantially greater than the network's $9.00 copay.

13. ADJOURNMENT – The meeting adjourned at 1200 hours. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland starting at 0800 on Thursday, 08 August 2002. All agenda items should be submitted to the co-chairs no later than 08 July 2002.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Pegfilgrastim injection (Neulasta; Amgen)	31 Jan 02; pegylated form of filgrastim (G-CSF) indicated to reduce the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving chemotherapy associated with a clinically significant incidence of febrile neutropenia.	**Note**: Filgrastim and Epogen are both on the NMOP covered injectables list. Added to the NMOP Formulary and Covered Injectables List	**Quantity Limits** 2 syringes per 45 day supply (NMOP); 1 syringes per 21 day supply (retail network). **Rationale for quantity limits:** Potential for excessive cost due to product wastage. **Prior Authorization:** None	Not added to the BCF **Similar BCF Drugs:** None
Comments regarding pegfilgrastim injection: Pegfilgrastim is given once per chemotherapy cycle as a single dose of 6 mg administered at least 24 hours after chemotherapy. Filgrastim is administered daily for up to 14 days following chemotherapy. Pegfilgrastim, at $1730/syringe, is somewhat more costly than a 10-day course of filgrastim at a daily dose of 300 mg per day ($1037) or 480 mcg per day ($1640). Because patients may decline further courses of chemotherapy due to unacceptable toxicity, the potential for product wastage is significant. Because pegfilgrastim should not be administered during the 14 days before chemotherapy because of the potential for an increase in the sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, it is not suitable for chemotherapy cycles much shorter than 21 days. A quantity limit of 2 syringes per 45 days (NMOP) or 1 syringe per 21 days (retail) allows a sufficient supply to cover the next chemotherapy cycle and a sufficient time to order the next needed dose				
Norelgestromin / ethinyl estradiol transdermal patch (Ortho-Evra; Ortho-Biotec)	20 Nov 01; prevention of pregnancy; first contraceptive available in a transdermal formulation; the ethinyl estradiol component is equivalent to 20 mcg of EE/day (low-dose estrogen). Norelgestromin is produced following oral administration of norgestimate, the progestin component found in Ortho-Cyclen and Ortho-Tricyclen.	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** None
Budesonide capsules (Entocort EC; Astra Zeneca)	02 Oct 01; glucocorticoid for the treatment of mild to moderate active Crohn's disease involving the ilieum and/or ascending colon (acute flares)	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** None

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Morphine sulfate extended release capsules (Avinza; Ligand)	20 Mar 02; launched on 2 May 02. Modified-release formulation of morphine sulfate intended for once-daily administration indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time; not intended for prn use.	Added to the NMOP Formulary.	**Quantity Limits:** General rule for Schedule II controlled substances applies; limited to 30 days supply at the NMOP **Rationale for quantity limits:** Existing quantity limits for Schedule II controlled substances **Prior Authorization** None	The current BCF listing for morphine sulfate extended release was clarified to exclude Avinza. **Similar BCF Drugs:** Morphine sulfate extended release (MS Contin and generic equivalents)
Olmesartan medoxomil (Benicar; Sanyko / Forrest)	25 Apr 02; approved for hypertension. This is the 7th Angiotensin Receptor Blocker (ARB) to be approved in the U.S.	Added to the NMOP Formulary.	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** None
Extended phenytoin sodium, 200 mg and 300 mg capsules (Phenytek; Bertek)	6 Dec 01; new branded formulation of phenytoin sodium indicated for the treatment of generalized tonic-clonic and complex partial seizures and prevention and treatment of seizures during or following neurosurgery 200 and 300 mg Phenytek capsules are bioequivalent to 2 and 3 Dilantin 100-mg capsules, respectively	Added to NMOP Formulary as a line extension.	**Quantity Limits** General rule applies **Prior Authorization** None	The current BCF listing for phenytoin oral was clarified to exclude Phenytek. **Similar BCF Drugs:** Oral phenytoin
Paroxetine controlled-release tablets (Paxil CR; GlaxoSmithKline)**)**	Approved for depression Feb 99 but not marketed until FDA approval for panic disorder was obtained in Feb 02. This new formulation of paroxetine does NOT extend the dosing interval (once-daily); a polymer matrix controls the dissolution rate over 4-5 hours and an enteric coating delays release until tablets have left the stomach, potentially improving tolerability. Because of reduced bioavailability, Paxil CR strengths are higher (12.5-, 25-, 37.5-mg) than Paxil immediate release (10-,20-,30-,40-mg).	Added to the NMOP Formulary	**Quantity Limits:** General rule applies **Prior Authorization:** None	The current BCF listing for paroxetine oral was clarified to exclude Paxil CR, pending a more thorough review in 6 months. **Similar BCF Drugs:** paroxetine, fluoxetine, citalopram, sertraline
Comments concerning paroxetine controlled-release tablets – The Committee agreed that information concerning the potential advantages of Paxil CR compared to immediate release paroxetine was not sufficiently complete to mandate that Paxil CR be added to all MTF formularies at this time. In addition, they wanted to obtain provider opinions concerning the utility of the new formulation that were not available at the time of the meeting. Paxil CR will be reviewed again in 6 months. It will be excluded from the BCF pending review.				

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. Additions to the BCF

   1) Combivent (ipratropium/albuterol sulfate) oral inhaler
   2) Raloxifene (Evista)
   3) Pseudoephedrine/Guaifenesin 600/120 mg extended release (Entex PSE equivalent).
   4) Levonorgestrel 0.75 mg (Plan B)—added to the BCF on 3 April 2002, but subsequently deleted from the BCF on 8 May 2002.

   B. Deletions from the BCF

   1) Propranolol LA
   2) Levonorgestrel 0.75 mg (Plan B)—deleted from the BCF on 8 May 2002

   C. Changes and clarifications to the BCF

   1) The current BCF listing for carbinoxamine/pseudoephedrine drops was changed to the "new" formulation (1 mg/15 mg per ml) since this is the only formulation available.

   A. Exclusions from the BCF

   1) Morphine sulfate extended release capsules (Avinza; Ligand)
   2) Extended phenytoin sodium, 200- and 300 mg capsules (Phenytek; Bertek)
   3) Paroxetine controlled-release tablets (Paxil CR; GlaxoSmithKline) – pending more thorough review in 6 months.

2. **NMOP FORMULARY CHANGES**

   A. Additions to the NMOP Formulary (See Appendix A for details)

   1) Pegfilgrastim injection (Neulasta; Amgen) – added to the NMOP Covered Injectables List. Quantity limits apply, see below
   2) Norelgestromin/ethinyl estradiol transdermal patch (Ortho-Evra; Ortho-Biotec) –
   3) Budesonide capsules (Entocort EC; Astra Zeneca)
   4) Morphine sulfate extended release capsules (Avinza; Ligand)
   5) Olmesartan medoxomil (Benicar; Sanyko/Forrest)
   6) Extended phenytoin sodium 200- and 300 mg capsules (Phenytek; Bertek)
   7) Paroxetine controlled-release tablets (Paxil CR; GlaxoSmithKline)

   B. Exclusions from the NMOP Formulary -None

   C. Clarifications to the NMOP Formulary - None

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**

   A. Quantity limit for Pegfilgrastim Injection (Neulasta; Amgen): 2 syringes per 45-day supply (NMOP); 1 syringe per 21-day supply (retail network).

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)** - None

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **7 May 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 7 May 2002 and from 0800 to 0815 hours on 8 May 2002 at the Officers Club, Fort Sam Houston, TX.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (Representing COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board

MEMBERS ABSENT

COL Rosa Stith, MC	Army

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC (P) Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
HM1 Lisa Drumm	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
CAPT Howard Hays, MD	USPHS/Indian Health Service
CAPT Samuel Hope	USPHS/Indian Health Service
CAPT Robert Pittman	USPHS/Indian Health Service
LCDR Thomas Berry	USPHS/Indian Health Service

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

Four members of the Indian Health Service (IHS) National Formulary Work Group attended the DoD P&T Executive Council meeting. The IHS is evaluating the feasibility of establishing a national formulary.

5. LEVONORGESTREL 0.75 MG (PLAN B)

At the February 2002 DoD Pharmacy & Therapeutics (P&T) Executive Council meeting, the Council recommended the addition of levonorgestrel 0.75 mg (Plan B) to the Basic Core Formulary (BCF), subject to the review and approval of the Director, TRICARE Management Activity (TMA) and/or the Assistant Secretary of Defense for Health Affairs (ASD (HA)). On 28 March 2002, the Executive Director of TMA signed an Action Memo approving the recommendation. On 3 April 2002 the co-chair of the DoD P&T Committee informed the Council members and service pharmacy consultants of the decision, and re-informed the Council on 7 May 2002. On 8 May 2002 the Executive Council was reconvened briefly to announce that the Council co-chairs had been informed that the ASD (HA) also wanted to review the Council's recommendation and that the Executive Director of TMA had rescinded his earlier approval. Therefore, Plan B has NOT been approved for addition to the BCF at this time, and the ASD (HA) is reviewing the Council's recommendation.

MTFs are required to include all BCF drugs on their local formularies. As a result of Plan B's removal from the BCF, each MTF's P&T committee must now re-evaluate whether this product is within the scope of practice at the MTF and whether the MTF wants to continue to have Plan B on its formulary.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

Contract awards, renewals, and terminations

- Contracts for oral contraceptives, etodolac, fexofenadine, hydrochlorothiazide, insulin needle/syringes, isosorbide mononitrate, capsaicin cream, and ticlopidine were renewed.
- New contracts were awarded for ibuprofen tablets and fluoxetine capsules.
- DoD contracts for lisinopril and hepatitis A are up for renewal.
- The following joint DoD/VA contracts are up for renewal: ointment base, carbidopa/levodopa SA; glyburide tablets, amantadine capsules, fluocinonide cream/ointment, terazosin tablets/capsules, sotalol tablets, bupropion tablets, acyclovir tablets/capsules, hydroxyurea capsules, pentoxifylline tablets, rifampin capsules, and sucralfate tablets.
- The following joint DoD/VA contracts are up for resolicitation: salsalate tablets, prednisone tablets, and cimetidine tablets.
- The following joint DoD/VA contracts are in various stages of solicitation: benztropine mesylate tablets, minoxidil tablets, carbidopa/levodopa IR tablets, famotidine, chlorpromazine tablets, thiothixene, penicillin VK tablets, dicloxacillin capsules, cephalexin capsules, amoxicillin capsules, and trihexyphenidyl.

7. REEVALUATION OF THE BASIC CORE FORMULARY (BCF)

A. BCF Objective – As outlined in HA Policy 98-034, the objective of the BCF is to ensure the uniform availability of cost-effective pharmaceuticals at MTF pharmacies in order to meet the majority of patients' primary care needs. An analysis of prescriptions dispensed by MTF pharmacies between 1 Oct 01 and 15 Mar 02 revealed that 62% were for BCF items if prescriptions for OTCs were included, and 71% if OTC items were excluded. These data suggest that the BCF objective is being accomplished to a substantial degree.

Some people propose that a large number of drugs should be added to the BCF in order to retain and recapture prescription workload from retail pharmacies where the drugs cost more. This proposal assumes that the addition of a drug to the BCF will actually cause patients to get their prescriptions filled at an MTF rather than a retail pharmacy. Many factors influence patient behavior, so it is difficult to predict the impact that BCF status will actually have on the retention/recapture of prescription workload.

The Council faces a dilemma: Should inclusion on the BCF be reserved for only the more cost-effective drugs in an attempt to encourage the use of agents that offer the best overall value? Or should the Council simply ignore the BCF objective and add a bunch of drugs to the BCF (regardless of their cost-effectiveness) in the hope that it will help retain

and recapture workload from retail pharmacies? The Council did not reach a consensus on this issue.

B. *OTC Coverage on the BCF* – TRICARE policy provides limited coverage of OTC drugs at retail pharmacies and the NMOP. Chapter 7, Section 7.1 of the TRICARE Policy Manual states that: "Insulin and related supplies may be cost-shared for diabetic patients, regardless of whether or not a prescription is required under state law"; and "Vitamins may be cost-shared only when used as a specific treatment of a medical condition." Non-covered benefits include: "Drugs, including compounded preparations, that are available over the counter."

   Although TRICARE policy does not govern the availability of OTC products at MTF pharmacies, the Council has historically refrained from adding OTC products to the BCF. The BCF currently includes only 11 OTC items. The recently published Uniform Formulary Proposed Rule states, "The Basic Core Formulary (BCF) is a subset of the Uniform Formulary and is a mandatory component of all MTF pharmacy formularies". If the BCF is to be a subset of the Uniform Formulary, the inclusion of OTCs on the BCF will be limited by TRICARE policy.

   From 1 Oct 01 to 15 Mar 02, MTFs dispensed 3.7 million prescriptions for OTC drugs, which accounted for 16.3% of total prescriptions dispensed during that time period. The eleven OTC items on the BCF accounted for only 500,000 of the 3.7 million prescriptions for OTC drugs, so MTFs clearly provide many more OTC drugs than those included on the BCF.

   In light of the Uniform Formulary Proposed Rule, the Council unanimously voted not to add any additional OTC products to the BCF beyond those identified in the TRICARE Policy Manual. However, the Council encourages MTFs to continue providing OTC medications when they represent cost-effective alternatives to legend drugs. The Council will explore mechanisms other than the BCF to promote uniform availability of cost-effective OTC medication at MTFs.

C. *Comparison of the BCF to VA's National Formulary* - The term "formulary" most properly refers not only to a list of drugs on the formulary of a health care institution or system, but also to related information concerning the use of drugs and to the drug use policies of that institution or system as a whole. The BCF and the VA National Formulary (NF) have fundamental differences that reflect underlying differences in the MHS and VA drug delivery systems, despite similar underlying concepts—both are intended to make cost-effective drug therapies uniformly available across large health care systems. Formulary status on the BCF and/or the NF is increasingly being used to leverage lower prices for commonly used pharmaceuticals in classes where several therapeutically equivalent alternatives exist.

   One of the fundamental differences between DoD and the VA that affects formulary structure is the fact that VA facilities generally do not fill prescriptions from outside providers. The VA also lacks a full-service mail order point of service analogous to the NMOP (the VA Consolidated Mail Outpatient Pharmacy (CMOP) is used to expedite the processing of refills) and VA beneficiaries do not have the option of taking their prescriptions to retail network pharmacies. In addition to point of service and

administrative differences, there are well-known patient population differences between the two systems that may affect drug formularies.

DoD and the VA differ even when considering only MTFs and VA facilities, most notably in the degree to which local formulary decision-making is retained by individual facilities. In the VA, the NF is supplemented by 22 regional (VISN) formularies, but local formularies are forbidden and local formulary decision-making is restricted to antimicrobials (to accommodate local resistance patterns). The BCF is supplemented by both regional (in some cases) and local formularies; individual facilities typically have independent P&T committees that retain broad autonomy over local formularies and drug use policy.

The NF drug list contains 1214 items (individual listings) in 28 categories, while the BCF contains 176 items in 24 categories. These counts were based on using the VA classification system and the formularies as listed on the VA PBM and DoD PEC websites as of May 02, after adjusting both lists to use common terminology. The VA drug classification system was chosen for this comparison because it provides consistent categories for all items on both the NF and the BCF, including medical supply items.

Three major categories where the two formularies differ substantially are injectable medications, medical supply items, and OTC medications. The NF contains a large number of medications that have not been traditionally represented on the BCF, including 344 injectable medications, most of which are typically only used on an inpatient basis (compared to 7 on the BCF); 131 medical supply items, including syringes, dressings, IV supplies, catheters, etc. (compared to 2 on the BCF); and 185 OTC medications (vs. 11 on the BCF).

Even if injectable medications, medical supply items, and OTC medications are excluded, the NF still contains more line items than the BCF (570 vs.156). The difference can be broken down into three primary contributing factors:

1) The NF contains some categories, such as antimicrobials, central nervous system medications (including antidepressants and antipsychotics), and antineoplastics, which appear to contain virtually all commonly used drugs in those categories. This may be due to resistance concerns (as would be the case with antimicrobials) or to lack of therapeutic interchangeability of drugs in these categories. Some of these drugs may be subject to criteria for use.
2) The NF covers some types of drugs traditionally not well represented on the BCF because they are considered to be specialty drugs (e.g., antineoplastics, antivirals, diagnostic agents, topical anesthetics).
3) The NF tends to list more alternatives than the BCF even in commonly used drug classes listed on both formulary lists. For example, the NF lists 5 oral glucocorticoids while the BCF lists 2, and the NF lists 8 nonsteroidal anti-inflammatory drugs while the BCF lists 3.

8. DRUG USE AND EXPENDITURE REVIEW

The Council was unable to assess the FY 02 budget execution by MTF pharmacies because:

- Prime vendor data are missing for so many MTFs that expenditures cannot be accurately estimated.
- CHCS pharmacy cost reports are not uniformly available from MTF pharmacies.
- MTF pharmacy expenditures reported by the TMA resource management differ significantly from the pharmacy expenditures reported by the resource managers for the three services.

9. PENDING CONTRACT INITIATIVES

A. Status of Contracting Initiative for Leutinizing Hormone Releasing Hormone (LHRH) Agonists – The DoD and the VA have agreed in principle on pursuing a contract for a Leutinizing Hormone Releasing Hormone (LHRH) agonist. The solicitation will be for a 1 and 3 month product from the same manufacturer for the treatment of prostate cancer; other formulations and strengths will not be included. The solicitation is currently being written, but has not yet been released.

B. Status of Contracting Initiative for Nasal Corticosteroids – The DoD and VA issued a joint solicitation to select a single source for flunisolide nasal inhalers. This solicitation does not stipulate that the contracted drug will be on the BCF. The DoD and VA are also working on a joint solicitation for a once-daily nasal corticosteroid inhaler that will place the contracted product on the BCF.

C. Status of Contracting Initiative for Triptans – The DoD and VA are working on a joint solicitation that will comply with the Council's previous stipulation that any contracting initiative must either allow or require MTFs to have at least two triptans on their formularies.

10. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES

: COL Remund briefed the Council on the PEC's attempt to outline the process that the Council has been using to identify clinically acceptable contracting/formulary strategies for drug classes. The Council followed the process described in Appendix A to evaluate the following drug classes.

A. Statins – The current DoD statin contract will expire in February 2003. A joint solicitation with the VA for a follow-on contract is currently being considered. A high potency statin (simvastatin or atorvastatin) must be included on the BCF in order for patients to attain the LDL-cholesterol goals established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guideline. A low potency statin could also be included on the BCF if it would enhance the cost effectiveness of cholesterol-lowering therapy in the Military Health System. The following analysis focuses on the high potency statins.

Therapeutic Interchangeability: Although atorvastatin can achieve larger reductions in LDL-cholesterol than simvastatin, less than 10% of patients require the magnitude of LDL-cholesterol reduction that can only be achieved by atorvastatin. Some studies indicate that atorvastatin may not raise HDL cholesterol levels as much as simvastatin, but the Council doubted that any difference in the effect on HDL levels would significantly affect the therapeutic interchangeability of these drugs for most patients. Long-term clinical trials prove that simvastatin reduces cardiovascular morbidity and mortality. Similar evidence is not available for atorvastatin. There are no data that demonstrate significant differences in safety or tolerability between atorvastatin and simvastatin. The Council concluded that simvastatin and atorvastatin have a high degree of therapeutic interchangeability.

Clinical Coverage: Simvastatin and atorvastatin each have the capacity to satisfy the LDL-cholesterol reduction needs of at least 90% of the DoD population. Some patients may have a clinical need to use pravastatin because of its lower potential for drug interactions, but these patients comprise less than 5% of statin patients. Providers expressed a preference for having more than one statin on the BCF, but they did not provide a clinical justification for a second statin on the BCF. The Council concluded that either atorvastatin or simvastatin would provide adequate clinical coverage.

Provider Acceptance: Provider acceptance of simvastatin is clearly supported by the fact that simvastatin currently accounts for about 95% of all statin prescription fills at MTF pharmacies. Providers also expressed a willingness to use atorvastatin. Providers voiced strong opposition to any contract that would require patients to be switched from one statin to another statin. Opposition to switching patients is understandable because (1) approximately 150,000 patients had to switch statins after the DoD statin contracts were awarded in August 1999 and (2) approximately 100,000 patients had to switch statins after cerivastatin was withdrawn from the market in August 2001.

The Council voted unanimously to support any contracting/formulary strategy (to include a closed class contract) that places at least one high potency statin on the BCF and does not require patients to be switched from one agent to another. The Council also supports the inclusion of a low-potency statin on the BCF if it is projected to enhance the cost-efficiency of statin therapy.

B. *Angiotensin Receptor Blockers (ARBs)* –Seven ARBs are available: losartan (Cozaar, FDA-approved in Apr 95), valsartan (Diovan, Dec 96), irbesartan (Avapro, Sep 97), candesartan (Atacand, Jun 98), telmisartan (Micardis, Oct 98), eprosartan (Teveten, Oct 99), and olmesartan (Benicar, Apr 02). All the ARBs are FDA-approved for hypertension.

ARBs offer a slight clinical advantage (lower incidence of cough and angioedema) compared to angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of hypertension, but ARBs cost much more than ACEIs. The JNC-VI Guideline advises that ARBs should be reserved for hypertensive patients who are unable to tolerate ACEIs. ARBs are also used “off-label” for congestive heart failure (CHF) and prevention of renal disease progression in diabetics. Despite a recent ADA recommendation that an ARB should be used as first line therapy in type 2 diabetes with hypertension and

microalbuminuria or clinical albuminuria, many providers still think that ARBs should be reserved for second line therapy when patients experience adverse effects on an ACEI.

Despite their "second line" place in therapy, ARB purchases by MTFs increased about 56% from $9 million in FY 00 to $14 million in FY 01. A significant price reduction might be achieved through a contracting initiative that places one or more ARBs on the BCF.

Therapeutic Interchangeability

- *Hypertension*: The Council considered the information contained in a joint VA/DoD clinical review of the ARBs (published on the PEC website). The Council concluded that ARBs have a high degree of therapeutic interchangeability in the treatment of hypertension.
- *CHF*: The FDA has characterized valsartan as "approvable" for CHF in patients not receiving an ACEI or as a substitute for an ACEI (despite the FDA advisory committee recommendation against approval). The ELITE I study showed increased survival for CHF patients on losartan compared to an ACEI, but the larger ELITE II study showed no significant difference in all-cause mortality for patients on losartan compared to an ACEI. The RESOLVD trial was discontinued because candesartan was associated with an increase in hospitalizations and death compared to CHF patients treated with enalapril. A large CHF trial comparing candesartan to an ACEI (the CHARM trial) is underway. Data are not available for the other ARBs in the treatment of CHF. The Council decided that the data are insufficient to conclude that the ARBs are therapeutically interchangeable for CHF.
- *Prevention of renal disease progression in diabetics*: A FDA advisory committee concluded that the IDNT and IRMA-2 trials were suggestive of efficacy, but the data were insufficient to support approval of irbesartan for prevention of renal disease progression in patients with type 2 diabetes. An FDA advisory committee recommended approval of losartan for the prevention of renal disease progression in diabetics based on the RENAAL trial. Data are not available for the other ARBs for this indication. The Council decided that the data are insufficient to conclude that the ARBs are therapeutically interchangeable for prevention of renal disease progression in diabetics.

Clinical Coverage: There is no evidence that if a hypertensive patient fails therapy with one ARB, a better response would occur with another ARB. Any of the ARBs would probably provide adequate clinical coverage when used for hypertension, but there are no data to support a conclusion that one or more of the ARBs is sufficiently safe, tolerable, and effective to satisfy the clinical needs of at least 90% of the patients when used for CHF or prevention of renal disease progression in diabetics.

Provider Acceptance: Losartan, valsartan, and irbesartan account for about 90% of prescription fills for ARBs at MTF pharmacies, and providers expressed a preference for these three ARBs. Nephrologists and endocrinologists prefer irbesartan and losartan. Cardiologists prefer valsartan. These three have been on the market longer than the other ARBs, so providers have more confidence in their safety profiles. Providers were uniformly opposed to switching patients from one ARB to another.

The Council unanimously voted to add at least one ARB to the BCF in an open class, with guidelines for appropriate use. The Council also stipulated that any contract for an ARB should not require patients to be switched from one ARB to another ARB.

C. *Thiazolidinediones (TZDs, "glitazones")* – While the TZDs offer a relatively modest reduction in HbA1C compared to other antidiabetics, diabetic patients frequently require combination therapy with two or more agents. Even small reductions in HbA1C correlate with a decreased risk of microvascular complications. There has now been sufficient clinical experience with TZDs to lessen the concern regarding hepatoxicity. The VA is currently considering adding a TZD to its National Formulary. A DoD and VA joint procurement strategy for TZDs might achieve a substantial price reduction.

Therapeutic Interchangeability: There are no large, randomized, controlled head-to-head trials comparing rosiglitazone (Avandia) and pioglitazone (Actos). However, comparison of clinical trial data suggests that they reduce HbA1C by the same degree when equivalent doses are used (pioglitazone 45 mg qd = rosiglitazone 4 mg bid, or pioglitazone 30 mg qd = rosiglitazone 8 mg qd). Both drugs are approved for monotherapy and for use in combination with metformin or a sulfonylurea. Pioglitazone is approved for use with insulin, and the FDA has classified rosiglitazone as "approvable" for use with insulin. There are case reports of heart failure occurring with both drugs when used in combination with insulin. There is insufficient evidence to conclude that the drugs differ in their propensity to cause or exacerbate heart failure.

Comparison of data from clinical trials suggests that pioglitazone has a more favorable effect on LDL-cholesterol and triglycerides than rosiglitazone. However, due to the significant intra-person and inter-person variability in lipid levels, the variability in methods used to measure lipid levels, and potential differences in study subjects across the trials, it is difficult to draw a definitive conclusion about any true differences in lipid effects. The clinical significance of the potential differences in lipid effects is also unknown. Table 1 shows the range of changes in mean lipid levels from clinical trials for rosiglitazone and pioglitazone.

Table 1: Range of Mean Lipid Changes from TZD Clinical Trials

	Rosiglitazone[a]	Pioglitazone[b]
LDL	↑ 5.3 – 22%	↑ 2.8 – 7.7%
HDL	↑ 8.4 – 18%	↑ 9.1– 15.8%
Triglycerides	↑9 – 19.6%	↓ 9.6 – 15.9%

[a] Rosiglitazone LDL results from 7 studies, HDL results from 5 studies, and triglyceride results from 2 studies.
[b] Pioglitazone results from 5 studies.

Rosiglitazone and pioglitazone appear similar to placebo in their propensity to cause elevation in liver transaminases. There are no data to suggest that they differ significantly in their potential to cause hepatotoxicity, edema or weight gain.

Clinical Coverage: Based on their FDA-approved indications, either of these drugs can be expected to have the desired clinical effect in over 90% of patients.

Provider Acceptance: Providers would generally accept either agent, but some indicate a preference for pioglitazone due to its more favorable lipid profile. PDTS prescription data

show that pioglitazone has consistently increased its share of prescription fills for TZDs across all three outpatient pharmacy points of service over the past year.

Council members had difficulty reaching consensus on whether this class is suitable for a closed class contract. Objections to a closed class contract centered on the potential lack of therapeutic interchangeability between pioglitazone and rosiglitazone in regard to their effects on LDL-cholesterol and triglycerides. Some Council members also expressed concern that the potential for discovery of new clinical information about these drugs makes a closed class contract risky for this drug class. After two motions failed, the Council approved a third motion to add one TZD to the BCF via a procurement initiative that leaves the TZD class open and does not require patients to be switched from one TZD to another.

11. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *COX-2 Selective Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)* – The major advantage of COX-2 selective NSAIDs ("COX-2 inhibitors") compared to non-specific NSAIDs is a reduced incidence of complicated upper gastrointestinal (GI) events (GI bleed, perforation, and obstruction) and symptomatic but uncomplicated ulcers. Evidence that COX-2 inhibitors actually provide this benefit is primarily derived from two large trials: the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) and the Celecoxib Long-term Arthritis Safety Study (CLASS).

VIGOR demonstrated a statistically significant reduction in the annualized incidence of complicated upper GI events in patients receiving rofecoxib (0.6%) vs. naproxen (1.4%), which equates to a number-needed-to-treat (NNT) of 125. In other words, 125 patients would need to be treated with rofecoxib rather than naproxen for one year to prevent one complicated upper GI event. CLASS (celecoxib vs. ibuprofen and diclofenac) failed to demonstrate a statistically significant reduction in complicated upper GI events for its overall patient population, but a statistically significant reduction in complicated upper GI events did occur in the subgroup of patients not receiving aspirin. A statistically significant reduction also occurred for the broader endpoint of complicated upper GI events plus symptomatic but uncomplicated ulcers regardless of aspirin use.

If the reduction in complicated upper GI events in VIGOR is generalized to all COX-2 inhibitors and the daily cost of COX-2 inhibitor and nonspecific NSAID therapy is estimated to be $1.50 and $0.15, respectively, treating 125 patients for one year with COX-2 inhibitors rather than nonspecific NSAIDs would prevent one complicated GI event at an incremental drug cost of about $61,600. This does not take into account the effect of reductions in the incidence of symptomatic but uncomplicated ulcers and possibly in the incidence of GI symptoms and the use of medications to treat GI symptoms (e.g., H2-blockers and PPIs).

Because the risk of NSAID-associated GI events is known to differ among patient populations (based on factors such as age, use of other medications that increase GI risk, use of prophylactic medications, and history of peptic ulcer disease and/or prior GI events), the NNT from the VIGOR trial and the associated cost to prevent one GI event cannot be generalized to all patients. The NNT and the associated costs would be much higher in a patient population without known risk factors (e.g., young patients, many of

whom would receive relatively short-term treatment with NSAIDs) than in the patient population studied in VIGOR (older RA patients requiring chronic NSAID therapy).

Estimates of the background risk of GI events in a general patient population are not readily available. However, if the baseline annualized risk of NSAID-associated GI events in such a patient population is assumed to be about 0.5%, and the relative reduction in events with COX-2 inhibitors vs. nonspecific NSAIDs is assumed to be similar to the reduction in VIGOR (about 50%), the NNT would be 400. Using the same daily medication costs described above, 400 patients would have to be treated for one year with COX-2 inhibitors rather than nonspecific NSAIDs to prevent one complicated GI event, at an incremental drug cost of $197,000.

COX-2 inhibitors appear to be somewhat better tolerated with regard to dyspepsia and other GI symptoms than the non-specific NSAIDs to which they have been compared. COX-2 inhibitors appear similar to non-specific NSAIDs in regard to other adverse effects (e.g., renal adverse effects and propensity to cause edema and blood pressure elevation). COX-2 inhibitors do not affect platelet aggregation.

The VIGOR trial demonstrated a statistically significant increased risk in serious cardiovascular (CV) thrombotic events (primarily acute myocardial infarctions) in patients treated with rofecoxib compared to patients treated with naproxen (1.1% vs. 0.5%). The cause of this finding, its potential applicability to other COX-2 inhibitors, and its real meaning in day-to-day clinical practice are subject to considerable debate. Subsequent analyses of pooled data comparing rofecoxib to NSAIDs other than naproxen or to placebo have not shown an increased in CV risk for rofecoxib.

COX-2 inhibitors do NOT appear to be any more effective than non-specific NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, or dysmenorrhea.

After reviewing the clinical data, the Council reiterated its conclusion that even if COX-2 inhibitors are used only in patients at increased risk for NSAID-associated GI events, the DoD would incur a large increase in drug costs for a rather small decrease in GI events. If COX-2 inhibitors are used in patients with a “normal” risk for GI events, the DoD would incur huge incremental costs for miniscule incremental benefits. The Council acknowledged that the COX-2 inhibitors are being considered for addition to the BCF because of the potential financial impact of shifting prescriptions from the retail network to MTFs—not because of the clinical value they offer in comparison to their cost.

To estimate the potential for increased use of COX-2 inhibitors if a COX-2 inhibitor were added to the BCF, the PEC compared COX-2 inhibitor prescription fill rates (as a percent of all Rx fills) at MTFs that have one or more COX-2 inhibitors on formulary to MTFs that do not have a COX-2 inhibitor on formulary. Assuming that the prescription fill rates at sites that do not currently have a COX-2 inhibitor on formulary would increase to the same rate as sites that do, the total number of COX-2 Rx fills at MTFs would increase by 180,000 per year (32.8%) if a COX-2 inhibitor were added to the BCF. This increase would inevitably include use of COX-2s in both patients likely to benefit (i.e., long-term use in patients with risk factors for GI complications) and patients unlikely to benefit (short-term use in patients without risk factors) from using COX-2 inhibitors.

At the last meeting, the Council asked DSCP to issue a request for Blanket Purchase Agreement (BPA) price quotes to the pharmaceutical companies that market COX-2 inhibitors for the purpose of adding a COX-2 inhibitor to the BCF in an open class. The request for BPA price quotes also asked companies to submit their plans for assisting MTFs in targeting the use of COX-2 inhibitors to the patients at greatest risk for GI events. The VA decided not to participate in this BPA request for quotes.

The Council evaluated the projected weighted average daily cost per patient that would result from the price quotes offered for each COX-2 inhibitor. The Council also used a mathematical model to estimate the potential financial impact of adding each COX-2 inhibitor to the BCF. The model took into account likely increases in use and projected shifts in utilization amongst the three points of service. After evaluating a variety of scenarios, the Council concluded that it was in the best interest of the government not to accept any of the BPA price quotes, so a COX-2 inhibitor was not added to the BCF.

B. Raloxifene (Evista) – Raloxifene was evaluated for potential addition to the BCF based on high retail network use. PDTS data from July through December 2001 showed 37,200 prescriptions for 13,000 unique patients in the retail network, with an annual cost to DoD of $5 million.

Raloxifene is the first of a new class of agents known as selective estrogen receptor modifiers (SERMs). A derivative of tamoxifen, raloxifene has a mixed agonist-antagonist effect on estrogen receptors throughout the body. It is indicated for the prevention and treatment of osteoporosis in postmenopausal women. Alendronate, also approved for the treatment of osteoporosis, is currently on the BCF.

The most common side effects of raloxifene are hot flashes and leg cramps. Patients treated with raloxifene were at higher risk of venous thromboembolism (NNH 143) than the placebo group. The increased risk is similar to the risk of venous thromboembolism seen with hormone replacement therapy (HRT). In the MORE trial, raloxifene reduced the risk for new vertebral fractures by 50% in women without previous fractures (NNT 46) and by 30% in those with previous fractures (NNT16). Both reductions were statistically significant. Raloxifene also increased BMD of the femoral neck and spine by 2-3%. The drug cost to prevent one vertebral fracture in 3 years is $42,000 compared to a cost of $27,000 for alendronate to prevent one vertebral fracture in 3 years.

Raloxifene's nonskeletal effects include reductions in LDL cholesterol (11%) and total cholesterol (7%), without changes in HDL cholesterol. Raloxifene reduced the risk of invasive breast cancer by 76% in the MORE trial. Studies are underway to investigate the cardiovascular benefits of raloxifene and to compare it to tamoxifen in the prevention of breast cancer.

Providers and pharmacists were surveyed regarding their use and potential use of raloxifene. Eighty-five responses were obtained. All responses favored the addition of raloxifene to the BCF. Raloxifene 60 mg is currently on the formulary of approximately 20% of MTFs.

The Council voted to add raloxifene to the BCF.

C. *Calcium (calcium and calcium + vitamin D)* – Given the Council's previous decision not to add any OTC medications to the BCF beyond those identified in the TRICARE Policy Manual, the Council did not consider the proposal to add calcium and calcium + vitamin D to the BCF. The Council acknowledged that clinical data fully support the use of calcium in patients with osteoporosis and especially in patients treated for osteoporosis with prescription medications. The Council encourages all MTFs to make available and promote adequate calcium supplementation in patients for the prevention and treatment of osteoporosis.

D. *Guaifenesin/pseudoephedrine sustained release tablet (generic Entex-PSE)* – Entex-LA eq. (guaifenesin & phenylpropanolamine long-acting) was removed from the BCF at the Nov 00 P&T Committee meeting because of safety concerns expressed by the FDA regarding phenylpropanolamine. The Committee had intended to select an alternative agent for the BCF after manufacturers reformulated their products, but an alternative agent was not selected. The PEC recently identified that guaifenesin (GFN) and pseudoephedrine (PSE) long-acting, the logical replacement for Entex-LA eq., was the second most prescribed non-BCF drug. Many different brands and formulations exist (e.g., Entex-PSE, Duratuss, Deconsal-II), but MTFs overwhelmingly use the GFN 600mg/PSE 120mg formulation. Three manufacturers currently offer prices of less than $0.07 per tablet for this product. The Council unanimously voted to add GFN 600 mg/PSE 120 mg long acting to the BCF.

12. CLARIFICATION OF BCF LISTING

Carbinoxamine/pseudoephedrine (Rondec) Drops — Lt Col Zastawny presented a clarification of the BCF listing of carbinoxamine/pseudoephedrine drops. A recent formulation change for the branded product (Rondec®) decreased the concentrations of the ingredients from 2mg carbinoxamine and 25mg of pseudoephedrine per mL to 1mg carbinoxamine and 15 mg of pseudoephedrine per mL. Changes were also made in the recommended dosing schedule included with the product. The new 1mg/15mg per mL formulation appears to be the only formulation currently being produced by the brand and generic manufacturers. The change in recommended dosing raises concern about the potential for dosing errors resulting in excessive dosing of pseudoephedrine in pediatric patients if the two dosage forms were used interchangeably.

The Council agreed to (1) specify the newer carbinoxamine 1mg and pseudoephedrine 15mg per mL formulation on the BCF, 2) remove the Rondec® brand name reference from carbinoxamine/pseudoephedrine drops listing on the BCF, and 3) provide a link from the BCF listing to a drug and dosing information page.

13. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove propranolol LA from the BCF* – A request to delete propranolol long-acting (LA) from the BCF cited lack of generic availability and low utilization. The PEC confirmed the shrinking availability of generic forms of propranolol LA. Approximately 4000 patients use propranolol LA. The number of unique users has remained relatively constant over the past three years. The Council voted to delete propranolol LA from the BCF because of decreasing generic availability and availability of preferable alternatives on the BCF (e.g., metoprolol, atenolol).

B. *Request to add Combivent (18 mcg ipratropium/103 mcg albuterol) MDI to the BCF –* An Air Force pulmonologist provided the following rationale for the request:

- Seven studies have shown that the addition of an anticholinergic with a beta agonist can achieve enhance bronchodilation.
- Patients with COPD (stage II and III) are required to take both medications. Combivent is included as the standard of care in the VHA/DoD, ATS, and new GOLD guidelines for the management of COPD.
- Compliance with a MDI increases when only one device or inhaler is used and guarantees the patient receives both medications for maximal effect.

Safety and tolerability of the combination product are similar to the same dosages of the products administered by separate inhalers. Combination therapy with ipratropium and albuterol has been shown to produce superior bronchodilation without additional side effects compared to monotherapy with albuterol or ipratropium. In stage II and III COPD, a combination of ipratropium plus a beta-agonist is associated with lower rate of exacerbations and lower total health-care costs than compared to albuterol or ipratropium monotherapy. Efficacy of Combivent is similar to the same dosages of the ipratropium and albuterol administered by separate inhalers.

The PEC requested provider (physician and pharmacist) input on this issue and received 33 responses: 26 favoring, 5 against, and 2 inconclusive regarding addition of Combivent to the BCF. Providers made several key points:

- This medication is used in patients with COPD, who frequently are noncompliant and smoke. They need the ipratropium to assist with lung function, but they don't necessarily feel the effect like they do with albuterol.
- Each inhaler requires 2 inhaled puffs 3-5 minutes apart, and to do both albuterol and ipratropium at a time would take up to 20 minutes, which most patients are not willing to do. Combivent only takes 3-5 minutes, and they won't get the two confused.
- The addition of Combivent to the BCF may improve patient satisfaction and compliance.
- Although we see a fair amount of civilian prescriptions, it is not on our MTF formulary. If it is cheaper for us to fill than the Tricare network, than I guess that would be a positive.
- There is a potential to reduce waste and pharmacy labeling costs from the use of two products.

Prime vendor data show that nonavailability of the contracted brand of albuterol MDI causes MTFs to actually pay more than the contract price for albuterol MDIs. FSS and contract pricing as of April 02 for Combivent and the individual products compared to the MTF average price paid (Nov 01- Jan 02) are presented in the following table:

Item Description	Doses/container	FSS Price As of April 02	MTF Ave Price (PV data Nov 01 – Jan 02)
Albuterol MDI	200	$ 1.65 (Contract price as of Nov 01)	$ 3.26
Ipratropium MDI	200	$ 19.59	$ 18.82
Combivent MDI	200	$ 22.47	$ 21.59

The cost of Combivent is compared to the cost of the individual products using both lowest available FSS price and MTF average price in the following table:

	Combivent cost/day 2 puffs four times daily	Cost/day of equivalent dose of individual products	Additional cost per day for Combivent
FSS Price	$ 0.90	$ 0.85	$ 0.05
MTF Ave Price	$ 0.86	$ 0.88	($ 0.02)

Combivent is on approximately 53% of MTF formularies. It ranks #25 in total MTF prescription fills of legend drugs that are not currently on the BCF. Combivent also falls in the top 100 prescriptions filled in the retail network.

Addition of Combivent to the BCF could improve patient satisfaction and compliance. There is also a potential reduction in waste. There is a potential for cost savings to the government since the average MTF price for Combivent is $0.02/day less expensive than the cost/day of equivalent dose of individual products. The Council voted to add ipratropium/albuterol (Combivent) to the BCF.

C. *Request to remove Fosamax 5 and 10 mg from the BCF* – The PEC received a request to remove the 5 mg and 10 mg strengths of alendronate, citing low usage of the daily dosage forms of these agents since the weekly forms became available. In general, the BCF listing of a drug includes all formulations and dosage strengths. The Council found no compelling reason to change the listing for alendronate, and voted unanimously to retain alendronate 5 mg and 10 mg on the BCF. Individual MTFs must make the drug available, in all strengths, when needed. Decisions about stocking levels may be made at the MTF level based on usage at that facility.

14. ADJOURNMENT

The meeting adjourned at 1600 hours on 7 May 2002. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland at 0800 on 7 August 2002. All agenda items should be submitted to the co-chairs no later than 8 July 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Appendix A: Drug Class Evaluations to Determine Clinically Acceptable Contracting/Formulary Strategies

1. The DoD P&T Executive Council evaluates the relative safety, tolerability, efficacy, price/cost and other pertinent issues ("STEPO" evaluation) to assess three factors that affect the acceptability of various contracting/formulary strategies:

   a. *Therapeutic interchangeability*: Therapeutic interchangeability is the extent to which drugs have similar clinical attributes, are used for the same indications, are used for the same patient populations, and can be expected to achieve similar clinical outcomes. Closed class contracts that require patients to be switched to the contracted drug require the highest degree of therapeutic interchangeability.

   b. *Coverage of clinical needs*: The drug(s) selected for a closed class contract must be sufficiently safe, tolerable, and effective to satisfy the clinical needs of at least 90% of the patients for whom the drug will be prescribed. Too many patients and providers will be forced to use the non-formulary/special order process if fewer than 90% of the patients can be successfully treated with the contract drug.

   c. *Provider acceptance*: Provider acceptance is the extent to which DoD providers are willing to use the contracted drugs and refrain from using the non-contracted drugs. There are two components to this condition. The first relates to provider behavior when first starting a patient on one of the agents in the class. For some drug classes providers will not accept a requirement to prescribe a particular agent even though it has been determined to be therapeutically equivalent to other members of the class. This is often true of newly approved drugs, but may apply to other members of the class as well. A lack of long-term safety data is a common cause for this concern. The second component relates to whether prescribers are willing to switch patients currently being treated with one drug in a class to the contract winner following contract award. Willingness to switch is tied to the perceived likelihood that the contracted drug will effectively substitute for the patient's current therapy and the amount of effort it takes to make the switch.

2. The DoD P&T Executive Council then decides which (one or more) of the contracting/formulary strategies described below are clinically acceptable and specifies any "clinical imperatives" that must accompany a given strategy. The VA/DoD Pharmaceutical Contracting Workgroup decides which specific contracting strategy to use from among the strategies that are acceptable to the DoD P&T Executive Council. Potential contracting/formulary strategies include the selection of one or more drugs for:

   a. A closed class contract that puts the contracted drug(s) on the BCF and requires patients to be switched to the contract drug(s).

   b. A closed class contract that puts the contracted drug(s) on the BCF, but does not require existing patients to be switched to the contracted drug(s).

   c. A closed class contract that does not put the contracted drugs(s) on the BCF, but requires existing patients to be switched to the contract drug(s).

   d. A closed class contract that does not put the contracted drugs(s) on the BCF and does not require existing patients to be switched to the contract drugs.

   e. A contract that puts the contracted drug(s) on the BCF but leaves the class open.

   f. The BCF based on an evaluation of the responses to a Blanket Purchase Agreement (BPA) request for price quotes

   g. The BCF based on a BPA(s) offered by one or more companies

   h. The BCF based on existing BPA(s)

   i. The BCF based on existing FSS prices

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MCCS-GPE **13 FEBRUARY 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0800 hours on 13 February 2002, at the Non-Commissioned Officers Club, Fort Sam Houston, TX

2. MEMBERS PRESENT

CDR Terrance Egland, MC, USN	DoD P& T Committee Co-chair
Col John R. Downs, MC	Air Force
Col Mark Nadeau, MC (For Col Bill Sykora, MC)	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
MAJ Brett Kelly	Army
LTC (P) Joel Schmidt, MC	Army
CAPT Robert Rist	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
William Hudson	Humana
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Dick Rooney	Department of Veterans Affairs

MEMBERS ABSENT

COL Daniel D. Remund, MS, USA	DoD P& T Committee Co-chair
COL Rosa Stith, MC	Army
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board
Ray Nan Berry	Health Net Federal Services

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Joe Torkildson, MC, USN	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC, USN	DoD Pharmacoeconomic Center
LCDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, USAF BSC	DoD Pharmacoeconomic Center
LTC Doreen Lounsbery, MC, USA	DoD Pharmacoeconomic Center
Maj Barb Roach, USAF MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS, USA	Defense Supply Center Philadelphia
CDR Brian Kerr, MSC, USN	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Vincent Valinotti	Defense Supply Center Philadelphia
David Chicoine	Uniformed Services Family Health Plan
Mark Petruzzi	Merck-Medco
Elizabeth Scaturro	Merck-Medco Managed Care

3. **REVIEW MINUTES OF LAST MEETING / ADM INISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **INTERIM DECISIONS** – No interim decisions.

5. **REPORT FROM THE DOD EXECUTIVE COUNCIL MEETING –** CAPT Torkildson reported on the additions to the BCF:

   - Advair (fluticasone/salmeterol) Inhaler: all strengths
   - Prempro (conjugated estrogen and medroxyprogesterone): all strengths.
   - Zithromax (azithromycin) 250 mg tablets; does not require the Z-pak dosage formulation.

6. **IMPLEMENTATION OF PHARMACY BENEFIT PROVISIONS IN THE FY00 AND FY01 NATIONAL DEFENSE AUTHORIZATION ACTS** - COL Davies will present the proposed rules at the next meeting if the document has been published. COL Davies stated that Managed Care Support Contractors have submitted nominations for providers to the DoD P&T Committee.

7. **PPI UTILIZATION IN THE NMOP** – CAPT Torkildson reported on proton pump inhibitor (PPI) use in all three points of service. There was a substantial decrease in the number of PPI prescriptions filled at MTFs during the Thanksgiving and Christmas holiday seasons, which raises questions regarding access. The total number of prescriptions for PPIs filled in the NMOP remains fairly flat while the retail network is showing a gradual growth rate. An analysis of the market share of the various PPIs by point of service reveals an increase in rabeprazole (Aciphex) use in the MTFs,

while the retail network analysis reveals a growing use of esomeprazole (Nexium) and stable use of omeprazole. The market share of omeprazole in the NMOP remains high at around 75% of all PPI prescriptions, with a slight upward trend in esomeprazole use. An analysis of the average cost per unit for PPIs for each point of service shows that the cost has declined by over 50% in MTFs, has remained flat in the retail network, and increased in the NMOP due to an omeprazole price increase. The Committee took no action on this information, but will continue to monitor the class.

8. **GENERIC LOVASTATIN IN THE NMOP** –The impact of the recent approval of a generic formulation of lovastatin on the current statin contract and the potential for creating patient dissatisfaction regarding the current structure of copays was discussed. The situation has been created in which a patient might submit a prescription for lovastatin to the NMOP in order to obtain the $3.00 generic copay, only to be told that they must use the contracted drug simvastatin and pay a $9.00 copay. COL Davies stated that it is not within the purview of this committee to reduce the co-pay for simvastatin to the generic copay since it did not compete directly against generic products. In a closed class contract, medical necessity is required in order to go outside the contract. When presented with a statin prescription other than simvastatin, the NMOP should call the provider and determine if there is a medical necessity for the noncontracted statin. If not, the contract situation should be explained to the provider, and an opportunity presented to switch to simvastatin. If the provider is not willing to change the prescription, the prescription should be returned to the patient and their options explained to them.

9. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 13 new drugs (see Appendix A).

10. **ANTIBIOTIC PROPHYLAXIS FOR ANTHRAX EXPOSURE** – CAPT Torkildson reported that the utilization of doxycycline and ciprofloxacin at the NMOP and in the retail network has returned to baseline levels. The Committee concluded that there is no further need to report on this subject unless subsequent events create the possibility of change.

11. **PRIOR AUTHORIZATIONS**

A. *Cost avoidance from NMOP prior authorizations (PAs)* – Shana Trice (PEC) reported that, for the 1st quarter of FY 02, the NMOP PAs for sildenafil, COX-2 inhibitors, and etanercept resulted in an estimated cost avoidance per new prescription submitted of $51.91 for sildenafil, $15.64 for COX-2 inhibitors, and $276.74 for etanercept. The estimated cost avoidance per new prescription submitted is based on the cost avoidance model outlined in the Aug 00 DoD P&T Committee minutes. Since these estimates are consistent with previous reports, the Committee did not make any changes to these PAs.

B. *Changes to PA criteria for COX-2 inhibitors* – The Committee addressed two issues: 1) a new FDA-approved indication for celecoxib (Celebrex) for acute pain in adults and treatment of primary dysmenorrhea; and 2) the availability of a new COX-2 inhibitor valdecoxib (Bextra). The FDA approved valdecoxib in Nov 01 for treatment of osteoarthritis (OA), adult rheumatoid arthritis (RA), and primary dysmenorrhea.

Existing NMOP PA criteria for COX-2 inhibitors allow use of rofecoxib but not celecoxib for 20 days or less in patients with risk factors for GI adverse events, since celecoxib previously lacked any indication for acute use. The Committee approved the following revised COX-2 inhibitor criteria for all COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib):

- *Benefit coverage NOT provided for:*
    - *Concurrent anti-inflammatory therapy with any NSAID or aspirin at doses > 325 mg per day, or*
    - *The prevention of colon cancer, or*
    - *The prevention or treatment of Alzheimer's disease*
- *Benefit coverage provided for:*
    - *Patient has previously failed an adequate trial with at least two different NSAIDS,*

      OR
    - *COX-2 therapy AND high risk for NSAID-induced gastropathy OR use of a NSAID could result in destabilization or risk. Identified by an of the following:*
        - *Concurrent oral corticosteroids, anticoagulants, antiplatelet agents*
        - *History of PU*
        - *History of NSAID related ulcer*
        - *History of clinically significant GI bleeding*
        - *Hereditary or acquired coagulation defect*
        - *Age 65 years or older*

C. *Criteria for etanercept PA* – The FDA recently approved psoriatic arthritis as a new indication for etanercept (Enbrel). The Committee voted to add this indication to etanercept's PA criteria.

D. *Anakinra (Kineret)* – This is a new IL-1 receptor antagonist product with a mechanism of action similar to the TNF receptor antagonist etanercept. However, it differs from etanercept in its FDA approved indications (see Appendix A), and therefore requires a separate PA. The Committee voted to adopt the Merck Medco criteria currently in place:

1. Coverage provided for the treatment of moderately to severely active rheumatoid arthritis in patients ≥ 18 years of age.
2. Coverage provided in situations where the use of methotrexate and at least one other DMARD have failed to treat the patient's rheumatoid arthritis.
3. Coverage provided in situations where the patient has had an inadequate response to methotrexate, unless the use of methotrexate is contraindicated for the patient.
4. Benefit coverage not provided for use of anakinra in combination with etanercept or infliximab.

The Committee discussed quantity limits for anakinra, given the exiting 6-week quantity limits in the NMOP for etanercept. They felt that, given the similarities between etanercept and anakinra, it would be most appropriate to apply the same quantity limits to both drugs. The

Committee established a 6-week quantity limit was established for anakinra in the NMOP and a 4-week supply in the retail network. The reason for the quantity limit is the same for both etanercept and anakinra: potential for significant unnecessary expense resulting from discontinuation, given the extremely high unit cost of these medications.

12. SUBCOMMITTEE REPORT: PROVISION OF INJECTABLE DRUGS IN THE NMOP OR RETAIL NETWORK PHARMACIES – Tabled until the May DoD P&T Committee meeting

13. CONTROLLED DISTRIBUTION OF PEGINTERFERON ALFA 2B (PEG-INTRON; SCHERING) – LCDR Briski reported that the distribution process has been complicated due to the unexpected demand for Peg-Intron. A formal understanding with Schering has been reached. Currently, any new patients will go onto a waiting list. The wait is expected to be one to two months. All current patients will be provided product to complete their course of therapy. LCDR Briski provided an outline of the current distribution method:

- New patients should be instructed to call the Schering 800 number to get on the waiting list. The patient will be called when it is their turn to move off the list and be instructed to take their prescription to the MTF pharmacy. All new starts, as they move off the wait list, will receive product via a drop-ship to MTF mechanism, which will be billed through Prime Vendor.
- Any current patients should complete their therapy by continuing to use their current mechanism for acquiring the drug. If the patient was enrolled into the "Assured Access" program and assigned an identifying number, they should complete their course using that mechanism. Sites that have been getting the Peg-Intron drop-shipped without registering the patient should continue to do so. As the current patients using assured access identifiers complete their therapy, the need for using the numbers will also go away.
- LCDR Briski is the point of contact for distribution issues. The PEC will provide a monthly report to Schering regarding the number of MTF patients receiving Peg-Intron so Schering can reconcile this with the amount of product shipped. If an imbalance occurs, the PEC will clarify the situation by contacting the MTFs involved directly.

14. ADJOURNMENT – The meeting adjourned at 1200 hours. The next meeting will be held at the Non-Commissioned Officers Club, Fort Sam Houston, TX starting at 0800 on Wednesday, 09 May 2002. All agenda items should be submitted to the co-chairs no later than April 8, 2002.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Valdecoxib tablets (Bextra; Pharmacia)	19 Nov 01; COX-II inhibitor for treatment of signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA), and for the pain associated with menstrual cramping	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization:** Add to (NMOP only) COX-2 inhibitor PA as modified in the Feb 02 DoD P&T Committee minutes. **Rationale for PA:** The COX-II inhibitors celecoxib and rofecoxib require prior authorization in the NMOP. The potential for inappropriate use is substantial.	Not added to the BCF **Similar BCF Drugs:** none
Frovatriptan tablets (Frova; Elan)	09 Nov 01; 5HT agonist ("triptan") for the treatment of migraine with and without aura in adults	Added to the NMOP Formulary	**Quantity Limits** 9 tablets per 30 days; 27 tablets per 90 days; consistent with existing quantity limits for other triptans **Rationale for Quantity Limits:** Clinical appropriateness concerns: potential for overuse and increased likelihood of rebound headaches **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** Sumatriptan
Desloratadine tablets Clarinex; Schering-Plough)	21 Dec 01; non-sedating 2nd-generation antihistamine for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and older	Added to the NMOP Formulary **Note**: Closed class contract is in place for 2nd generation NSA (fexofenadine) in the MTFs, but it does not apply to the NMOP. Three other 2nd generation products are currently available through the NMOP.	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** Closed class contract exists for fexofenadine (Allegra) that includes BCF status.

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Anakinra injection (Kineret; Amgen)	14 Nov 01; interleukin-1 receptor antagonist administered subcutaneously for the reduction in signs and symptoms of moderately to severely active RA in adult patients who have failed one or more disease modifying antirheumatic drugs (DMARDs)	Added to the NMOP Formulary and Covered Injectables List **Note**: Etanercept for RA is included in the NMOP Covered Injectables List, subject to quantity limits and prior authorization	**Quantity Limits:** 6-weeks **Rationale for quantity limits:** Extremely high unit cost increases negative impact of premature discontinuation. **Prior Authorization** Yes, approved use of PA criteria already established by Merck Medco.	Not added to the BCF **Similar BCF Drugs:** none
Comments about anakinra injection: Can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents [etanercept (Enbrel); infliximab (Remicade)]. Potential for serious infections and neutropenia is increased when used in combination with TNF blocking agents; combination use is not authorized in current PA criteria. Injection site problems are very common (71% of patients) upon initiation of therapy.				
Triptorelin pamoate depot injection (Trelstar LA; Debiopharm/ Pharmacia)	Jun 01; injectable leutinizing hormone releasing hormone (LHRH) agonist administered every 3 months for the treatment of advanced stage prostate cancer. Product is extension of previously approved one-month product, Trelstar Depot	Added to the NMOP Formulary and Covered Injectables List **Note**: Other depot LHRH agonists (Lupron and Zoladex) are included on the NMOP Covered Injectables List. Both 1-month and 3-month products added	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** none
Fondaparinux injection (Arixtra; Sanofi/Organon)	11 Dec 01; injectable factor Xa inhibitor (different than a low - molecular-weight heparin [LMWH]) for the prevention of venous thromboembolism following orthopedic surgery (knee replacement, hip replacement, hip fracture repair)	Added to the NMOP Formulary and Covered Injectables List **Note**: Injectable LMWHs are included on the NMOP Covered Injectables List	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** none
Comments about fondaparinux injection: The Committee discussed the fact that the current BCF mandates MTFs to have at one LMWH (enoxaparin, dalteparin, tinzaparin) on their formulary; individual MTFs choose which LMWH to have on formulary. Fondaparinux is not a LMWH and is not yet approved for outpatient treatment of VTE. The Committee determined that fondaparinux would not be considered a suitable substitution for one of the other LMWH products.				

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Pimecrolimus 1% cream (Elidel; Novartis)	13 Dec 01; treatment of mild to moderate atopic dermatitis in patients aged two years and older	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** See comments
Comments about Pimecrolimus 1% cream: There are no non-steroidal topical immunomodulators (TIMS) currently on the BCF. The BCF does include a medium potency steroid agent (triamcinolone acetonide 0.1% cream; Kenalog) and a high potency steroid agent (fluocinonide 0.05% cream; Lidex).				
Diclofenac sodium topical gel (Solaraze; Sky Pharma)	23 Oct 00; treatment of actinic keratoses; topical NSAID	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF Drugs:** None
Dexmethyl-phenidate tablets (Focalin; Novartis)	13 Nov 01; d-isomer of methylphenidate administered twice daily for the treatment of attention deficit hyperactivity disorder; not an extended or sustained release product	Added to the NMOP Formulary	**Quantity Limits** Standard NMOP rule for Schedule II products for treatment of ADHD applies– up to 90 day supply, no refills **Rationale for Quantity Limits: F**alls under standard rule in NMOP for Schedule II products for treatment of ADHD **Prior Authorization:** None	Not added to the BCF **Similar BCF Drugs:** Methylphenidate, methylphenidate SR and methylphenidate extended release (Concerta)
Comments about dexmethylphenidate tablets: The pharmacokinetic properties of the isomer are sufficiently different such that the FDA considers dexmethylphenidate to be a new drug. Therefore, it should not be considered the same as methylphenidate. There is no evidence that this is a significant advance in therapy for ADHD. A head-to-head trial against other forms of methylphenidate (instead of placebo) would help to clarify its place in therapy. It is specifically excluded from the BCF listing for methylphenidate.				

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Bosentan tablets (Tracleer; Actelion)	20 Nov 01; non-selective endothelin receptor antagonist for the treatment of pulmonary artery hypertension	NOT Added to the NMOP Formulary **Note**: Not feasible to provide bosentan through the NMOP due to its restricted distribution process	**Quantity Limits** N/A **Prior Authorization** Need to coordinate with TRICARE	Not added to the BCF **Similar BCF Drugs:** none
Comments about bosentan tablets: Although bosentan will be used in only a limited number of patients; it needs to be available to DoD beneficiaries. There are approximately 1,900 patients in the DoD with a diagnosis of PAH, but the severity of disease cannot be determined. Bosentan cannot be added to the NMOP due to the closed distribution system initiated by the manufacturer. The limited distribution system is due to the potential toxicities (hepatic and fetal) of this agent. Bosentan will be made available upon referral from specialty care physicians. When the distribution process is finalized, it will be disseminated via the service pharmacy consultants.				
Lovastatin/niacin tablets (Advicor; KOS)	18 Dec 01; combination of a statin and extended release niacin for the treatment of 1° hypercholesterolemia and mixed dyslipidemia who require additional lipid modification for LDL and HDL cholesterol and triglycerides beyond that achieved by the individual components	NOT Added to the NMOP Formulary	**Quantity Limits** N/A **Prior Authorization** N/A	Not added to the BCF **Similar BCF Drugs:** Closed class contract exists for simvastatin (Zocor)
Comments about lovastatin/niacin tablets: Addition of Advicor to either the BCF or NMOP formulary would be a violation of the simvastatin contract. Advicor should be available through the NMOP only in cases of documented medical necessity.				
Extended phenytoin sodium, 200 mg and 300 mg capsules (Phenytek; Bertek)	6 Dec 01; New branded generic formulation of phenytoin sodium indicated for the treatment of generalized tonic-clonic and complex partial seizures and prevention and treatment of seizures during or following neurosurgery 200 and 300 mg Phenytek capsules are bioequivalent to 2 and 3 Dilantin 100-mg capsules, respectively	Automatic addition to NMOP Formulary as line extension	**Quantity Limits** General rule applies **Prior Authorization** None	Need to clarify whether the current BCF listing for phenytoin oral will include Phenytek. This issue was tabled until pricing and provider input is available.
Brimonidine tartrate ophthalmic solution (Alphagan P; Allergan**)**	Reformulation of brimonidine tartrate ophthalmic solution with a different preservative, a lower concentration of brimonidine, and a modified pH	Added to the NMOP Formulary Conversion from Alphagan 0.2% to Alphagan P 0.15% is expected due to the planned phase out of Alphagan P 0.2%.	**Quantity Limits** General rule applies **Prior Authorization** None	Added to the BCF **Clarification:** The BCF listing will be clarified to identify brimonidine 0.15% (Alphagan P) as the specific agent on the BCF for the reasons outlined in the comments below.
Comments about brimonidine tartrate ophthalmic solution: Alphagan P 0.15% provides comparable IOP-lowering efficacy to Alphagan 0.2% (potentially due to increased bioavailability of the purite formulation as demonstrated in animal studies). No clinically significant differences were found in mean IOP or mean change from baseline in IOP between the two formulations. The incidence rate of allergic conjunctivitis in the Alphagan P 0.15% group was 41% less than in the Alphagan 0.2% group. Both products are used BID 95% of the time vs. the TID package insert recommended dosing. Company plans on phasing out the Alphagan 0.2%.				

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. *Additions to the BCF*

      1) Advair (fluticasone/salmeterol) Inhaler: all strengths

      2) Prempro (conjugated estrogen and medroxyprogesterone): all strengths.

      3) Zithromax (azithromycin) 250 mg tablets, does not require the Z-pak dosage formulation.

      4) Plavix (clopidogrel) *[NOTE: Clopidogrel added to Appendix B subsequent to the initial release of these minutes on 8 Mar 2002. Please see Section 11 of the Feb 02 DoD P&T Executive Council meeting minutes.]*

   B. *Deletions from the BCF*

      None

   C. *Changes and clarifications to the BCF*

      1) The current BCF listing for brimonidine tartrate ophthalmic solution was clarified to identify the new Alphagan P 0.15% formulation as the specific agent included on the BCF.

2. **NMOP FORMULARY CHANGES**

   A. *Additions to the NMOP Formulary* (See Appendix A for details)

      1) Valdecoxib tablets (Bextra; Pharmacia) – added to NMOP with PA criteria

      2) Frovatriptan tablets (Frova; Elan) – quantity limits apply, see below

      3) Desloratadine tablets (Clarinex; Schering-Plough)

      4) Anakinra injection (Kineret; Amgen) –added to NMOP Covered Injectables List with PA criteria, quantity limits apply, see below

      5) Triptorelin pamoate depot injection (Trelstar LA; Debiopharm/Pharmacia) – added to NMOP Covered Injectables List

      6) Fondaparinux injection (Arixtra; Sanofi/Organon) – added to NMOP Covered Injectables List

      7) Pimecrolimus 1% cream (Elidel; Novartis)

      8) Diclofenac sodium topical gel (Solaraze; Sky Pharma)

      9) Dexmethylphenidate tablets (Focalin; Novartis) – quantity limits apply, see below

      10) Extended phenytoin sodium, 200 mg and 300 mg capsules (Phenytek; Bertek) – automatic line extension

      11) Brimonidine tartrate ophthalmic solution (Alphagan P; Allergan) - with natural attrition from Alphagan 0.2% to Alphagan P 0.15%

   B. *Exclusions from the NMOP Formulary*

      1) *Bosentan (Tracleer; Actelion)* - excluded from the NMOP due to closed distribution system initiated by the manufacturer.

2) *Lovastatin/niacin (Advicor; KOS) sustained release tablets* – lovastatin is currently excluded as a formulary agent due to existing statin contract (simvastatin) that is in effect through Feb 02.

C. Clarifications to the NMOP Formulary

None

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**

A. Quantity limit for frovatriptan tablets: 9 tablets per 30 days; 27 tablets per 90 days; consistent with existing quantity limits for other triptans.

B. Quantity limit for anakinra injection (Kineret; Amgen): NMOP: 6 packs of 7 syringes per 6 weeks; Retail: 4 packs of 7 syringes per 4 weeks.

C. Quantity limit for dexmethylphenidate tablets: Standard NMOP rule for Schedule II controlled products for treatment of ADHD applies – up to 90 days supply, no refills

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)**

A. *Etanercept (Enbrel)* -The FDA recently approved psoriatic arthritis as a new indication for etanercept (Enbrel). The Committee voted to add this indication to etanercept's PA criteria.

B. *COX-2 Inhibitors* - The Committee voted to have the same PA criteria apply to all COX-2 Inhibitors. See Section 11B for revised PA criteria.

C. *Anakinara (Kineret)* - The Committee voted to adopt the Merck Medco criteria currently in place. See Section 11D, of minutes for PA criteria.

Department of Defense
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MCCS-GPE **12 February 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 12 February 2002 at the Non-Commissioned Officers Club, Fort Sam Houston, TX.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (Representing COL Bill Sykora, MC)	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
MAJ Brett Kelly, MS	Army
LTC (P) Joel Schmidt, MC	Army
CAPT Robert Rist	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
Dick Rooney	Department of Veterans Affairs

MEMBERS ABSENT

COL Rosa Stith, MC	Army
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC (P) Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol (select) Barb Roach, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
CAPT Andy Meadows, USAF	Lead Agent Region 6
Leticia Ramirez	Pharmacy Student, University of Texas at Austin Pharm.D. Program
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
CDR Brian Kerr, MSC	Defense Supply Center Philadelphia
Vincent Valinotti	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES

The Council approved the minutes of the last meeting with a correction in the last sentence of the fourth paragraph in section 10:

- Incorrect sentence: The percentage of *fatal bleeding episodes* was 2.2% for clopidogrel plus aspirin compared to 1.8% with aspirin plus placebo (a statistically non-significant difference).
- Corrected sentence: The percentage of *life-threatening bleeding episodes* was 2.2% for clopidogrel plus aspirin compared to 1.8% with aspirin plus placebo (a statistically non-significant difference).

4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

AMP funds will not be used to reimburse MTF pharmacies for pharmaceutical purchases in FY 02 because Program Budget Decision (PBD) 812 is supposed to provide sufficient funding for MTF pharmacies. PBD 812 provides MTF pharmacies with 15% more funding in FY 02 than was actually spent in FY 01.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

A. *Contract awards, renewals, and terminations*

- Contracts for Diltiazem XR, acetaminophen tablets, levobunolol ophthalmic solution, timolol ophthalmic solution, clotrimazole cream, and simvastatin were renewed.
- Contract for gemfibrozil was cancelled due to the manufacturer not being able to meet the terms of the contract.
- New contracts were awarded for cyclobenzaprine tablets, isosorbide dinitrate tablets, loperamide capsules, methocarbamol tablets, metoprolol tablets, verapamil immediate release tablets, and lactulose syrup, nitroglycerin patch, and glyburide micronized tablets.
- DoD contracts for lisinopril and hepatitis A are up for renewal.
- Joint DoD/VA contracts up for renewal: salsalate tablets, oral contraceptives, etodolac, fexofenadine, hydrochlorothiazide, insulin needle/syringes, isosorbide mononitrate, prednisone, capsaicin cream, cimetidine, ticlopidine, nicotine patches, and valproic acid.

B. *Status of Contracting Initiative for Leutinizing Hormone Releasing Hormone (LHRH) agonists* – CAPT Torkildson reported that the joint VA/DoD solicitation to select an LHRH agonist (for the treatment of prostate cancer only) has still not been released, pending completion of the update to the VA clinical review. The VA and AstraZeneca have agreed to further extend the VA's contract for Zoladex until such time as the joint VA/DoD contract has been awarded. AstraZeneca and TAP have indicated that the DoD Blanket Purchase Agreements (BPAs) for Zoladex and Lupron will remain in place until the new contract is awarded.

CAPT Torkildson presented an assessment of the clinical significance of the entry of triptorelin (Trelstar) into the LHRH agonist marketplace. Debio Recherche Pharmaceutique manufactures this agent in Switzerland; Pharmacia holds the marketing rights in the United States. This is another LHRH agonist that has been in use in Europe since 1985. The FDA approved the 1-month depot in June 2000; the 3-month depot was approved in June 2001. Both preparations are approved for the treatment of advanced prostate cancer. Unlike leuprolide and goserelin, triptorelin has no additional FDA-approved indications, although it is used in other countries for many of the same indications. Pharmacia has not yet begun marketing this product extensively in the United States. However, a company representative has indicated that they intend to bid on the joint VA/DoD LHRH agonist contract.

Two major clinical concerns have been raised regarding triptorelin. The first relates to the paucity of clinical trial data available for this agent. The majority of published reports were conducted and published in Europe in the mid to late 1980s. The primary study submitted for approval of the 3-month depot was an unpublished study that took place in South Africa. There are also no survival studies; efficacy was measured using the surrogate endpoint of a reduction in serum testosterone levels established as being equivalent to those seen following surgical castration. The second concern relates to the

drug's ability to continue to suppress testosterone production with repeated dosing, the so-called "acute on chronic effect". Following the initial dose of LHRH agonists, there is a surge in testosterone production that produces a disease flare in a small percentage of patients. This surge is followed by a predicable fall in serum testosterone concentrations to castrate levels. However, with some agents a second surge in testosterone production is seen following the second dose of the agent. This has led the FDA to require manufacturers of LHRH agonists to submit data with their approval applications regarding the likelihood that their product will induce this effect. Data were submitted for only 15/151 subjects enrolled in the South African trial noted above, 2/15 had secondary surges in testosterone levels above the acceptable level. As a result, in its approval letter the FDA has required the company to conduct a Phase IV pharmacology study to determine if this ratio is observed with a larger group of patients. While the clinical significance of this observation is unknown, it does create a concern regarding the ability of this agent to maintain serum testosterone levels within the range defined as acceptable.

The Council shared the concerns raised during the presentation, and voted unanimously that triptorelin should not be considered therapeutically equivalent to leuprolide and goserelin at this time. Triptorelin should not be included in a solicitation for a contract for an LHRH agonist for the treatment of prostate cancer.

C. *Non-sedating antihistamine contract* – Lt Col Zastawny informed the Council that prescriptions for fexofenadine (Allegra) continue to outnumber prescriptions for loratidine (Claritin) by a 9 to 1 margin at MTF pharmacies. The weighted average cost per tablet/capsule for non-sedating antihistamines purchased by MTFs in Dec 01 was $.53, which is 39% below the $.87 weighted average cost that existed prior to the contract.

According to Aventis, the 500 count bottles of both the 60 and 180 mg tablets will be added and the 60 mg capsules will be removed from the non-sedating antihistamine contract effective 28 Feb 2002. The contract price for the 60 mg and 180 mg tablets remains unchanged at $0.37 and $0.60 per tablet, respectively.

Cetirizine (Zyrtec) costs MTF pharmacies $.95 per day compared to only $.60 per day for fexofenadine 180 mg. MTFs fill almost as many prescriptions for cetirizine as for fexofenadine. The Council agreed that the PEC should publish an article in the PEC Update to encourage greater utilization of fexofenadine.

The FDA recently approved desloratadine (Clarinex). Desloratadine cannot be added to the BCF or MTF formularies while the contract for fexofenadine is in effect.

D. *Statin Contract* – MAJ Cheryl Filby stated that the contract for simvastatin (Zocor) was renewed for the final option year (until 19 Feb 03) as the Council recommended at the November meeting. Simvastatin and atorvastatin (Lipitor) account for 95% and 3.5% respectively of the total statin prescriptions filled at MTF pharmacies, but atorvastatin accounts for a much higher percentage at a few MTFs. An analysis of prescription data also revealed that the majority of atorvastatin prescriptions are filled for the 10 mg and 20 mg strengths. Higher dosages of atorvastatin (40 mg and 80 mg) would normally be needed if atorvastatin were used primarily for patients who failed to reach their LDL

goals on simvastatin. The PEC will provide statin usage data to MTFs and publish an article in the PEC Update that addresses the appropriate use of non-contracted statins.

E. *Status of contracting initiative for nasal corticosteroid inhalers* - The Council reiterated that neither flunisolide nor budesonide would be acceptable as the only nasal corticosteroid on the BCF because they too frequently require dosing more than once daily. The Council agreed that DoD could participate in a solicitation that may result in the addition of flunisolide or budesonide to the BCF, but neither of these drugs can be the sole nasal corticosteroid on the BCF.

F. *Potential contracting initiative for carbamazepine* – There is an opportunity to establish a joint VA/DoD single-source contract for an AB-rated generic carbamazepine. A recent analysis of carbamazepine purchases by DoD MTFs revealed that 85% of purchases were for branded Tegretol, at 5 times the cost of the available generics.

At the last DoD P&T Executive Council meeting, the PEC was asked to query the field and evaluate why there is high usage of brand name Tegretol when AB-rated generics are available. The Council also wanted a sense of how providers and pharmacists in the field would view a generic contract for this drug.

Responses were received from 35 primary care providers, pharmacists and neurologists. The majority of respondents (77%) were not concerned about whether the drug provided at their facility was generic or brand name. They agreed that Tegretol was prescribed because they were confident it would always be supplied by the same manufacturer. This guaranteed that the color, shape, etc. of the tablet would remain constant so as not to confuse patients or bring up questions of differences in bioavailability. Many also noted that carbamazepine is typically not the drug of choice for treating seizure disorders since safer options are now available. The drug is being used frequently for neuropathic pain control, where bioequivalence does not carry the same significance as it might for seizure control. However, since there is still some use as an antiepileptic, respondents felt a contract for an AB-rated generic would be acceptable, as long as a single manufacturer was chosen for a long-term contract to maintain consistency.

The Council learned that the proposed contract would allow facilities to use either the contracted generic or brand name Tegretol. The Council recognized that this conflicts with the desire of DoD providers to stipulate the use of a single carbamazepine product throughout the MHS. Some Council members asserted that this situation was still preferable to the current situation in the DoD, where all five generic products are currently being utilized. They also recognized the value in participating with the VA in a contracting action for this agent, and felt that it would be a first step in working toward the goal of all facilities using the contracted agent exclusively. After much discussion, the Council voted to support a joint VA/DoD solicitation for a single source of generic carbamazepine that allows MTFs to use either the contracted generic carbamazepine or brand name Tegretol (assuming that Tegretol does not in fact win the contract).

a. *Compliance with sole source contracts* - LCDR Ted Briski reported that a review of generic contract compliance revealed many instances where MTFs purchased non-contracted products. A small sampling of MTF pharmacy directors indicated that unavailability of the contracted product from the prime-vendor caused MTFs to purchase

non-contracted products. The Council views unavailability of contracted products as a patient compliance/safety issue since it may cause patients to receive different looking tablets or capsules each time they receive a prescription. LCDR Briski and Dave Bretzke will coordinate with MAJ Cheryl Filby to assess the problem and report back at the next meeting.

G. *Potential contracting initiative for fluoroquinolones* – Levofloxacin is currently on the BCF in accordance with a BPA. The Council concluded in Nov 01 that levofloxacin and gatifloxacin are therapeutically interchangeable and that either agent would be clinically acceptable as the "workhorse" oral fluoroquinolone. Ortho-McNeil has offered a modified BPA to both DoD and the VA, which removes the market share requirements and gives a uniform price of $2.00/tab system-wide. The BPA would reduce overall expenditures while avoiding the logistical and economic consequences of undergoing a product conversion that could potentially result from a contracting action. However, the Council also believes that it is still clinically acceptable to participate in a joint DoD/VA contract. Since the clinical needs of patients could be satisfied with either a contract or a BPA, the Council voted to support whichever joint action the VA/DoD contracting workgroup decides to pursue.

H. *Potential contracting initiative for triptans* – Lt Col Zastawny presented information from clinical studies and provider input regarding triptans. Clinical studies show that triptans generally will provide pain relief within 2 hours for 50-75% of patients and that 25-40% of patients will be pain free after two hours. One study showed that 45-58% of patients who did not respond to the initial triptan would respond to a different triptan. The clinical trial data suggest that patients' clinical needs would not be satisfied if a contract prohibited MTFs from having more than one triptan on their formularies. The majority of MTF providers surveyed by the PEC agreed that a contracting action would not be acceptable if it limited MTF formularies to a single triptan. The Council voted to support any contracting initiative or other pricing agreement that either allows or requires MTFs to have at least two triptans on their formularies.

I. *Potential contracting initiative for angiotensin receptor blockers (ARBs)* – LCDR Briski reported that MTF expenditures for ARBs increased from $5.7 million in FY 99 to $14.5 million in FY 01. The VA and DoD are working together on a clinical review of the ARBs. The PEC will forward the clinical review to Council members and compile additional information that will assist the Council in assessing the need for addition of an ARB to the BCF and the therapeutic interchangeability of the ARBs for a potential contracting initiative.

J. *Other contracting initiatives:* According to prime vendor data, national pharmaceutical contracts produced $16 million in cost avoidance at MTFs during the first quarter of FY 02. As for the third and fourth quarters of FY 01, prime vendor data for the first quarter of FY 02 are missing for many MTFs, so the actual cost avoidance is more than $16 million. Through Dec 01, the weighted average cost per unit for drugs covered by national pharmaceutical contracts is 33% less than the weighted average cost per unit that existed before the contracts took effect. Although MTFs are now spending much less for

proton pump inhibitors, no cost avoidance is attributed to this drug class because there is no contract in effect for proton pump inhibitors.

6. POTENTIAL IMPACT OF NEW GENERICS

A. *Fluoxetine:* CAPT Torkildson presented an update on the situation regarding generic fluoxetine. Barr Pharmaceuticals' 6-month period of exclusivity for this product expired in late January. On January 29 the FDA approved several additional generic fluoxetine products. At least two companies receiving approval have submitted the necessary paperwork to establish FSS pricing for their generic products. The prices contained in the most recent FSS pricing database for these products range from $4.49 to $5.19/100 capsules for the 10 mg and 20 mg strengths. It is uncertain at this time how soon these prices will be loaded or when they will be available to the MTFs, but they will likely be available by March 1. MTFs are advised to examine the available prices carefully before purchasing quantities of fluoxetine in the near future. If MTFs transition quickly to these significantly less expensive generic products, it is anticipated that the MHS could reduce expenditures for fluoxetine by as much as $13M over the next 12 months.

B. *Metformin:* The FDA approved generic formulations of metformin (Glucophage) on 25 Jan 01. At least six generic companies will market metformin, and five of them have approval for all three strengths (500-, 850-, and 1000 mg). The extended release metformin preparation (Glucophage XR) and combination product with glyburide (Glucovance) are still under patent.

Current FSS prices for Glucophage are $0.32 for the 500 mg tablet, $0.55 for the 850 mg tablet, and $0.58 for the 1000 mg tablet. MTFs spent approximately $20 million on Glucophage during the past 12 months. While FSS prices have not yet been established for generic metformin, a hypothetical example can illustrate the magnitude of potential cost savings. For example, MTFs could potentially save about $15 million annually if the generic metformin price is 75% less than the Glucophage price.

7. SUBCOMMITTEE REPORT: OBTAINING INPUT FROM PROVIDERS

LCDR Briski reported on the latest efforts by the PEC staff to obtain input from MTF-based providers, which is an important factor in pharmaceutical contracts and formulary management. The email groups put together by MAJ Roach have been effective, but do not reach all MTFs. Since the DoD P&T is a TMA chartered organization, using the TMA infrastructure is a logical mechanism to communicate with MTFs. The PEC initiated monthly teleconferences with lead agent medical directors and lead agent pharmacists. The PEC's goal is to tap into the already existing networks these senior Lead Agency staffers have established. Close contact with the service-specific chains of command will continue to be maintained via the Chief Pharmacy and Chief Clinical Consultants to each Surgeon General. In addition, the PEC is exploring the options for creating a Chat room/Bulletin Board section of the PEC web site to facilitate consistent and timely communication. P&T minutes will continue to be distributed through service and TMA lanes.

8. MTF REQUESTS FOR BCF CHANGES

A. *Request to add Advair (fluticasone/salmeterol) to the BCF* – An Air Force allergist provided the following rationale for the request:

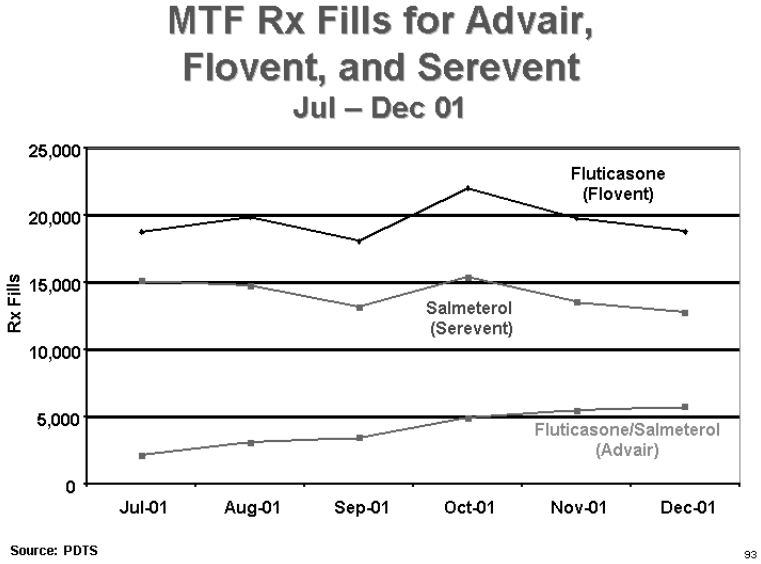
- Nine studies have proven that the addition of a long acting beta-agonist is superior to doubling the dose of inhaled corticosteroid (ICS) in the treatment of uncontrolled asthma in the patient already on an ICS.
- The evidence also suggests that long acting beta-agonists should never be used as mono-therapy and should always be used in conjunction with ICS.
- Compliance with asthma controller medication decreases when more than one inhaler is used.
- Advair offers mandatory combination therapy and a single inhaler of 1 puff twice a day (vs. 2 inhalers, 4 puffs twice a day).

Safety and tolerability of the combination product are similar to the same dosages of the products administered by separate inhalers. The FDA allowed the removal of the box warning about adrenal insufficiency surrounding the use of inhaled corticosteroids class because no cases were reported. Efficacy of the combination product is similar to the same dosages of the products administered by separate inhalers. An article by Aubier et al. comparing Advair vs. the two single agents demonstrated that the two arms were equal for morning Peak Expiratory Flow (PEF).

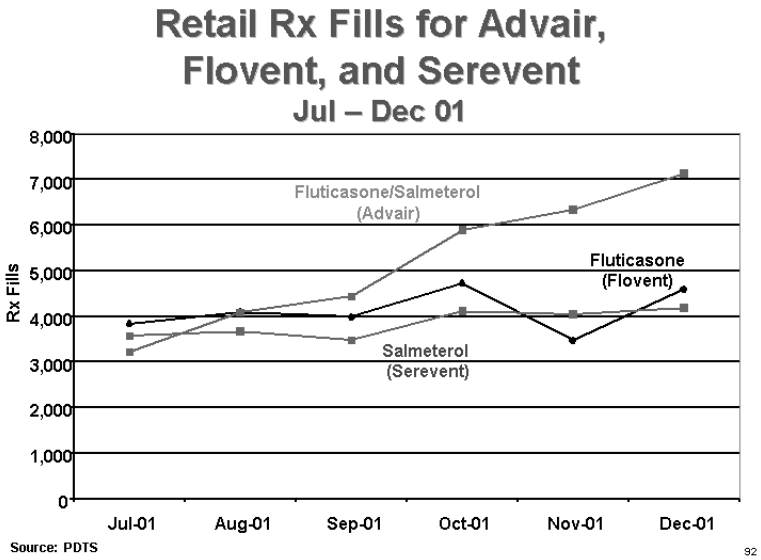
The PEC requested provider (physician and pharmacist) input on this issue and received 63 responses: 56 favoring addition to the BCF; 4 against addition to the BCF; and 3 inconclusive regarding addition of Advair to the BCF. Providers made several key points:

- Advair provides perceived symptom improvement within 30 minutes (from the Serevent). Researchers have speculated that the patient's perception of the benefit of the treatment rather than the dosage form itself may be the more critical factor. Some patients using the separate inhalers will identify Serevent as the agent that causes improvement, stop the inhaled steroid, and then end up on Serevent monotherapy. One large MTF survey showed that 200 patients were on Serevent monotherapy.
- The greatest benefit would be to our teenage population. The death rate of asthma in children has risen 150% between 1980 and 1996 – the age group with the highest mortality is 15-24 years of age. Asthma deaths today are preventable and we need to support combination therapy of inhaled corticosteroids and long-acting beta-agonists.
- Advair can be administered in 1/20 of the time it takes to use the 2 separate inhalers. How could this not improve compliance?

Fluticasone and salmeterol are on the BCF as individual agents. As shown in the following graph, prescription fills for Advair are rising steadily at MTFs (up 60% from Jul 01 to Dec 01), while usage of the individual agents is flat or declining slightly.



Prescription fills for Advair are rising even faster in the retail network pharmacies (more than doubled from Jul 01 to Dec 01)



The FSS pricing as of January 2002 for Advair and the individual products is presented in the following table:

Item Description		Doses/container	FSS Price As of Jan 2002
Advair Diskus Inhaler	fluticasone 100 mcg/salmeterol 50 mcg	60	$64.27
	fluticasone 250 mcg/salmeterol 50 mcg	60	$80.54
	fluticasone 500 mcg/salmeterol 50 mcg	60	$102.82
Serevent	salmeterol 25 mcg MDI	120	$42.72
	salmeterol 50 mcg diskus	60	$45.32
Flovent	fluticasone 110 mcg MDI	120	$39.60
	fluticasone 220 mcg MDI	120	$60.10

The cost of Advair is compared to the cost of the individual products in the following table:

Item Description	Advair cost/day Using twice daily dosing	Cost/day for equivalent dose of individual products	Additional cost per day for Advair
fluticasone 100 mcg/salmeterol 50 mcg	$2.14/day	$2.09/day	$0.05/day
fluticasone 250 mcg/salmeterol 50 mcg	$2.68/day	$2.43/day	$0.25/day
fluticasone 500 mcg/salmeterol 50 mcg	$3.43/day	$3.43/day	$0.00/day

Addition of Advair to the BCF could improve patient satisfaction and compliance. There is also a potential reduction in waste, since most fluticasone and salmeterol use is of MDI inhalers that are hard to estimate remaining doses. Advair Diskus gives number of doses remaining. The Council added all strengths of the fluticasone/salmeterol (Advair) to the BCF.

B. *Request to add Plan B (emergency contraceptive) to the BCF* – An MTF provider offered the following rationale in support of the request:

- Use of an emergency contraceptive is the only method available to prevent pregnancy after unprotected sexual intercourse or after a contraceptive "accident."

- It can provide emergency treatment for victims of sexual assault who were not protected by an effective contraceptive.
- A couple or a single female may suffer economic hardship as well as significant psychological and social costs from an unintended pregnancy.
- Although relatively higher in cost than some combination formulary contraceptives, the cost of Plan B is well within the range of the most commonly used preparations for this purpose, and the volume or frequency of use would be relatively low.
- The lower side effect profile of Plan B would decrease the use and cost of anti-emetics usually prescribed with the combination regimens, and the cost and necessity of return visits for adverse effects or therapeutic failure.
- The greater clinical efficacy, lower adverse effects, and simplified patient dosing regimen make Plan B the drug of choice for emergency contraception.
- Data indicate a rapid return of normal ovulation and fertility following discontinuation of either combined estrogen-progestin or progestin-only tablets for emergency contraception.
- Emergency contraceptives should be uniformly and immediately available in order to maximize their effectiveness in preventing unintended pregnancies and thereby reducing the number of women who seek elective abortions.

The Council considered the following information regarding emergency contraceptives in general and Plan B in particular:

- The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Practice (AAFP) recommend and endorse the use of emergency contraception.
- ACOG estimates that use of emergency contraceptives could prevent as many as half of the approximately 3 million unintended pregnancies that occur each year in the United States, including as many as 700,000 pregnancies that are terminated by abortion.
- Emergency contraception counseling should be provided during every annual health maintenance examination per BUMED NOTE 6320 (26 Oct 99) and Article 15-76 of the Manual of the Medical Department, Section VI; Family Planning, Contraceptive Counseling, and Sexually Transmitted Disease Prevention Counseling.
- The OB/GYN consultants for the three services support the addition of Plan B to the BCF.
- Ethics consultants for the three services concluded that there are no apparent reasons to preclude the use of Plan B at MTFs, since it is an FDA-approved contraceptive and not, as some argue, an abortifacient. Service regulations and TRICARE policy do not prohibit the coverage of emergency contraceptives. The presence of Plan B on the BCF would not "force" providers to prescribe Plan B. As with all other drugs on the BCF, the decision to prescribe Plan B would be left to the discretion of the individual provider.
- MTFs already provide emergency contraceptive therapy. Most MTFs use regular oral contraceptives in an "off label" fashion, while some MTFs use Plan B.
- The first dose of an emergency contraceptive should be taken within 72 hours of unprotected sex, preferably during the first 24 hours, followed by a second dose 12 hours later. The earlier the emergency contraceptive is given, the more likely it is to prevent pregnancy. The need for timely administration supports the argument that the emergency contraceptive should be on the MTF formulary in order to preclude delays that might

occur if the medication had to be obtained through a non-formulary or special order request.

- MTF providers and pharmacists responded to a survey regarding the proposal to add Plan B to the BCF. 38 respondents supported the addition, 15 respondents did not support the addition, and 14 respondents did not clearly express their position.
- Plan B is more efficacious than the Yupze regimen (ethinyl estradiol 100 mcg and levonorgestrel 0.5 mg taken twice, twelve hours apart). A large-scale clinical trial conducted at 21 treatment centers in 14 countries found a pregnancy rate of 1.1% (95% CI 0.6-2.0) for Plan B versus a pregnancy rate of 3.2% (95% CI 2.24.5) for the Yupze regimen.
- The incidence of nausea and vomiting associated with Plan B is less than half the incidence of nausea and vomiting associated with the Yupze regimen.
- The Plan B regimen requires the patient to ingest a total of 2 tablets, which is much more tolerable than the 20 tablets that a patient must ingest when using progestin-only tablets.
- The costs per regimen of the various emergency contraceptive alternatives are:
    - Plan B: $11.63
    - Preven: $3.91
    - Yupze regimen: $9.92
    - Progestin-only tablets (norethindrone): $9.20

The Council voted to add Plan B to the BCF. However, the Council decided that the addition of Plan B to the BCF would not be official until the Council verifies with TMA that this action is consistent with existing DoD policy.

9. REVIEW OF BCF

A. *Follow-up of anxiolytic review – potential BCF addition of venlafaxine extended release (Effexor XR)* – The Council recommended tabling this topic until the meeting in May.

B. *Analysis of midday dosing with methylphenidate dosage forms.* The following table displays the results of analyses of midday dosing associated with random samples of methylphenidate-SR prescriptions filled between Oct 99 and Sep 00 and Concerta prescriptions filled between Oct 00 and Dec 01.

Midday Dose	Methylphenidate-SR Rxs	Concerta Rxs
Yes	78 (40%)	17 (8%)
No	115 (60%)	178 (92%)
Total	193 (100%)	195 (100%)

The analyses indicate that the addition of Concerta to the BCF improved a humanistic outcome of drug therapy by decreasing the frequency of midday dosing of methylphenidate products for ADHD patients.

C. *Potential additions to BCF based on usage review*: Medications reviewed for BCF addition based usage criteria/analysis: 1) Top 200 list from PDTS; 2) High use in retail network; 3) Significant formulary status at MTFs; and 4) High dollar items.

- *Conjugated estrogens/medroxyprogesterone acetate (Prempro)* – Safety, tolerability and efficacy are similar for Prempro and the same dosages of the

drugs administered as separate tablets. Most providers think that the potential for improved compliance with Prempro may increase effectiveness. Based on prime vendor data, the average daily cost of Prempro is $0.32, while the average daily cost of providing the same dosage of medroxyprogesterone and conjugated estrogens via separate tablets is $0.39, so Prempro is actually less expensive than the individual products.

Prempro 0.625/2.5 is on the formulary at 63 (59%) of 107 MTFs. Prempro 0.625/5 is on formulary at 37 (35%) of 107 MTFs. Prempro 0.625/2.5 was ranked #5 in dollars spent, #24 in prescriptions, and #53 in unique users at retail network pharmacies.

The PEC requested provider (physician and pharmacist) input. Of 141 responses, there were 108 in favor, 17 opposed, and 16 indecisive regarding the addition of Prempro to the BCF.

The Council added all strengths of Prempro to the BCF.

- *Gabapentin (Neurontin)* – Gabapentin was evaluated for potential addition to the BCF based on the fact that gabapentin was in the top 200 in PDTS, high usage rate in retail network, and is a high dollar item. MTF expenditures for FY 01 were $12 million. Anticonvulsants rank #12 in all DoD expenditures, with ½ of that being gabapentin. Gabapentin 300mg strength ranks #17 in expenditures and #69 in unique users in the retail network.

  The PEC requested provider (physician and pharmacist) input on this issue and received 55 responses: 22 favored, 11 opposed (nearly all due to cost), and 12 were inconclusive regarding the addition of gabapentin to the BCF. One provider indicated that gabapentin quickly became a staple in their pain arsenal and usage would likely increase dramatically in the next few years. Another provider commented that the most beneficial aspects of gabapentin are its lack of significant interactions, lack of hepatic metabolism, and lack of need for blood work monitoring. A Pfizer report stated that the worldwide use for pain indication is 85% and is increasing by a 55% growth rate. Since the usage of gabapentin will likely continue to increase, and it is a safe, well-tolerated alternative to other agents for neuropathic pain control, the PEC recommended addition of gabapentin to the BCF.

  Council members were concerned that gabapentin is not FDA approved for pain control and that it may pose a large cost burden to small MTFs. They were also concerned that there is very little solid literature to back its use for pain control. The company has a supplemental new drug application pending for FDA approval for treatment of neuropathic pain.

  The Council decided not to add gabapentin to the BCF.

- *Azithromycin (Zithromax)* – Azithromycin is a widely used agent proven safe and effective in a broad range of infectious processes. FSS pricing as of Jan 2002 for the 250 mg strength of azithromycin is $4.00/tablet or $25.00/5 day course. Azithromycin 250 mg tablet strength is #2 by unique users and #9 by Rx fills in

the retail network. Azithromycin is on 94% of MTF formularies. Provider input was not obtained for this product. Due to high volume in retail pharmacy network and representation on a vast majority of MTF formularies the Council added azithromycin 250 mg tablets to BCF (does not require the Z-pak dosing form).

10. AVAILABILITY AND PRICING OF ORTHO NOVUM 7/7/7

Ortho Novum 7/7/7 is listed on the BCF and has been available for purchase by MTFs through the Depot or directly from Ortho-McNeil for approximately $7.70/cycle. This price is not available to MTFs via Prime Vendor (approximately $16.00/cycle) because of the packaging of the product ("clinic" packs vs. "commercial" packs). Ortho-McNeil stated that it would not renew the Depot contract, which expires at the end of February 2002. Ortho Novum 777 will no longer be available from the Depot when existing supplies are exhausted. There has been no determination on the long-term availability of the "clinic" packs directly from the manufacturer. The PEC will continue to monitor the situation and determine whether a change to the BCF is necessary.

11. BLEEDING RISKS IN THE CURE TRIAL

The Council evaluated the results from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial at the Nov 01 meeting in consideration of a proposal to add clopidogrel (Plavix) to the BCF. The Council noted the higher incidence of bleeding reported with the combination of clopidogrel plus aspirin vs. the placebo plus aspirin group. The definition of major bleeding used in the CURE trial differed from the widely accepted definition used by the American College of CHEST Physicians (ACCP). Council members were concerned that the number of major bleeds in the CURE trial may have been even higher if the ACCP definition had been used. The Council asked the PEC to request additional information from Bristol Myers Squibb (BMS) about the bleeding rates in the CURE trial.

The PEC sent questions to BMS on 3 Jan 2002. BMS referred the questions to the CURE trial investigators. The PEC received a response from the investigators on the evening of 11 Feb 02. The PEC did not have enough time to analyze the response prior to the 12 Feb 02 P&T Executive Council meeting. At the 12 Feb 02 meeting the Council asked the PEC to analyze the response, estimate the number of major bleeds using the ACCP definition for major bleeds, and forward the analysis and estimates to the Council members so they could vote on the proposal to add clopidogrel to the BCF and report the results of the vote as part of the minutes for this meeting.

Based on the response from the CURE investigators, the PEC estimated that the number of major bleeds in the clopidogrel plus aspirin group would increase by 6 (from 231 to 237) and the number of bleeds in the placebo plus aspirin group would increase by 9 (from 169 to 178) using the ACCP definition for major bleeds. Using the ACCP definition for major bleeds did not produce a significant change in the number of major bleeds for either group in the CURE trial. A BMS representative stated that several articles are planned for publication based on the CURE study, including one devoted to bleeding episodes. Additionally, newly updated guidelines by the American Heart Association and the American College of Cardiology are expected to recommend that clopidogrel receive a type one recommendation (the highest quality recommendation) for use in patients with non-ST segment-elevation myocardial

infarction; however, the guidelines have not yet been published. The PEC forwarded this information to the Council members, and the Council members voted to add clopidogrel to the BCF.

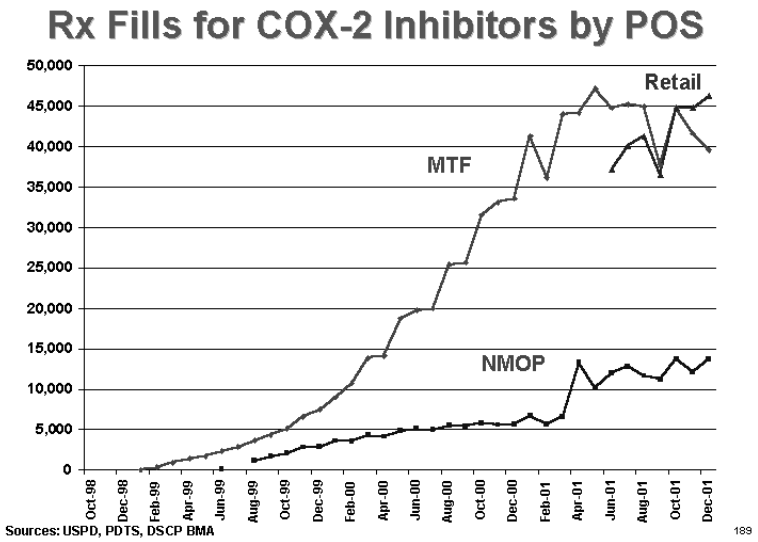
12. PROTON PUMP INHIBITORS

Rabeprazole (Aciphex) replaced omeprazole (Prilosec) on the BCF on 1 Oct 01. In Nov 01 the PEC asked MTF providers if there had been any specific problems with dosing, tolerance or patient response to Aciphex when used for common outpatient diagnoses such as GERD compared to their experience with Prilosec. Providers were also asked if the switch to Aciphex was problematic for providers, patients or pharmacists. The PEC received 41 provider responses from 32 MTFs. Most reported no problems and were very pleased with the huge decrease in the cost of proton pump inhibitor therapy. Favorable comments included the perception of a higher success rate with Aciphex and preference for the small Aciphex tablet compared to the large Prilosec capsule. A few providers reported a higher rate of treatment failures with Aciphex. One provider expressed concern about the procedure used by the MTF to convert patients from Prilosec to Aciphex.

13. COX-2 INHIBITORS

The Council considered various factors pertinent to the potential addition of a COX-2 selective inhibitor ("COX-2 inhibitor") to the BCF.

- COX-2 inhibitor usage data for the three outpatient pharmacy points of service are displayed in the graph below. After steadily increasing for 2.5 years, COX-2 prescription fills have leveled off at MTF pharmacies. COX-2 prescription fills have also leveled off somewhat in the NMOP after a sharp increase associated with the implementation of the TRICARE Senior Pharmacy Program. Limited historical data make it difficult to discern a usage trend in retail network pharmacies, but they are currently filling more COX-2 inhibitor prescriptions than MTF pharmacies.



- A survey of the COX-2 formulary status in the CHCS system at 96 MTFs revealed:
  - 41 (43%) had no COX-2 inhibitors on formulary
  - 30 (31%) had one COX-2 inhibitor on formulary
  - 25 (26%) had two COX-2 inhibitors on formulary
- Funding for MTF pharmacies in FY 02 is 15% above actual expenditures in FY 01. An objective of the increased funding is to make more drugs available at MTF pharmacies so that beneficiaries are not forced to go to a more expensive point of service (e.g. the retail network) to obtain their medications.
- Significant price reductions on certain drugs and the prospect for price reductions associated with the availability of new generic medications will substantially reduce MTF expenditures in some major drug classes, which can "free up" money for spending on other drug classes.
- A new COX-2 inhibitor, valdecoxib, is available. Approval of a fourth COX-2 inhibitor, etoricoxib, is expected in the near future. Significant price competition is unlikely at this time since the same companies that manufacture celecoxib and rofecoxib also manufacture the new agents, but more new entries in this and related drug classes are anticipated.
- The Council previously determined that celecoxib and rofecoxib are not sufficiently therapeutically interchangeable for a closed class contract.

The Council also reviewed a model constructed by the PEC that estimates the total cost to DoD of adding a COX-2 inhibitor to the BCF given assumptions about the percentage of switches from non-selective NSAIDs to COX-2 inhibitors, the absolute increase in COX-2 inhibitor prescriptions among patients not previously receiving an NSAID, the movement of COX-2 prescriptions from the retail networks to MTFs, and the anticipated percent decrease in average cost per unit for COX-2 inhibitors at MTFs and the NMOP that would result from selecting one COX-2 inhibitor for the BCF.

The Council voted that DSCP should issue a request for Blanket Purchase Agreement (BPA) price quotes to the pharmaceutical companies that market COX-2 inhibitors for the purpose of adding a COX-2 inhibitor to the BCF. The COX-2 drug class would remain "open" on the BCF. The Council will consider the price quotes, as well as the relative safety, tolerability, efficacy/effectiveness, and other relevant factors, in selecting a COX-2 inhibitor for the BCF. However, if its analysis demonstrates that it is not in the Government's best interest, the Council reserves the right to not select a COX-2 inhibitor for the BCF. The request for BPA price quotes will also ask the pharmaceutical companies to submit their plans for assisting MTFs in targeting the use of COX-2 inhibitors to the patients at greatest risk for gastrointestinal events. The Council encourages the continued use of COX-2 guidelines at MTFs in the efforts to ensure appropriate, cost-effective use of COX-2 inhibitors. The Council also requested DSCP to ask the VA if it wishes to participate in this request for BPA price quotes.

14. ADJOURNMENT

The meeting adjourned at 1600 hours on 12 Feb 2002. The next meeting will be held at the Non-Commissioned Officers Club, Fort Sam Houston, TX starting at 0800 on 8 May 2002. All agenda items should be submitted to the co-chairs no later than 8 April 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **15 NOVEMBER 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0800 hours on 15 November 2001, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL Mike Heath, MS (representing MAJ Brett Kelly)	Army
COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army
CAPT Chuck Bruner	Coast Guard
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
William Hudson	Humana
Ron McDonald	Sierra Military Health Services
Gene Lakey	TriWest

MEMBERS ABSENT

Dick Rooney	Department of Veterans Affairs
Ray Nan Berry	Health Net Federal Services

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
CAPT Betsy Nolan	Navy Pharmacy Specialty Leader
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
LCDR Denise Graham	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Maria Ionescu	Pharmacy Benefits Division, TMA
Howard Altschwager	Deputy General Counsel, TMA
David Bretzke	DoD Pharmacoeconomic Center
David Chicoine	Uniformed Services Family Health Plan
Lisa Le Gette	DoD Worldwide TRICARE Information Center
Shirif Mitry	Pharmacy Student, TMA
Mark Petruzzi	Merck-Medco
David Spiler	Merck-Medco
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

3. **REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES** – The Committee approved the minutes of the last meeting with one correction: the entry for valganciclovir (Valcyte) on Page 8 (Appendix A) was changed to list Roche as the manufacturer rather than Syntex.

4. **INTERIM DECISIONS** – In September 2001, voting members of the Committee communicated via email and telephone to make an interim decision regarding the status of PPIs on the National Mail Order Pharmacy (NMOP) Formulary subsequent to the expiration of the omeprazole contract on 1 Oct 2001. The voting members decided to retain omeprazole on the NMOP Formulary, add rabeprazole and pantoprazole to the NMOP formulary, and exclude lansoprazole and esomeprazole from the NMOP formulary. The decision was communicated to the field in early October 2001.

5. **UNIFORM FORMULARY–** COL Davies reported that the draft rule for the Uniform Formulary was sent to the Office of Management and Budget (OMB) on 29 Oct 01. [Note: It was subsequently determined that a summary notification of the draft rule was sent to OMB on 29 Oct 01. The draft rule was not sent to OMB until 30 Nov 01.]

6. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for 8 new drugs (see Appendix A).

7. **PROPOSED BPA FOR LANSOPRAZOLE FOR NMOP FORMULARY STATUS** - Lansoprazole (Prevacid) and esomeprazole (Nexium) are not on the NMOP formulary. TAP is offering a BPA with the following provisions if lansoprazole is added to the NMOP formulary:

   - For the first three months of the BPA (15 Nov 01 – 15 Feb 02), TAP will provide all eligible DoD MTF and NMOP facilities a $0.99 per tablet price for Prevacid.
   - Before the expiration of the first three-month period after pricing is in place, MTF and NMOP facilities must place Prevacid on their individual formularies in order to guarantee that they will continue to receive the BPA price for Prevacid.
   - If Prevacid has not been placed on individual MTF and NMOP formularies, TAP reserves the option to increase the price of Prevacid to the current published FSS price at MTFs where Prevacid is not on formulary.

   The Committee decided to place lansoprazole on the NMOP Formulary.

8. **PROPOSAL TO REMOVE OMEPRAZOLE FROM THE NMOP FORMULARY** – As of the first week in November 2001, the average cost per unit for proton pump inhibitors (PPIs) dispensed by the NMOP was $1.86, which is 72% higher than the $1.08 average cost per unit for PPIs dispensed by MTF pharmacies. MTFs and the NMOP pay the same prices for PPIs. The average cost per unit is higher in the NMOP because high-priced omeprazole continues to dominate PPI usage in the NMOP (72% of PPI prescription fills during the first week in November). Legal challenges continue to delay the availability of generic versions of omeprazole, so price relief is not imminent. A recent "Pink Sheet" article contained a prediction by a generic manufacturer that generic versions of omeprazole would not be available until the second half of calendar year 2002.

   The P&T Committee considered a proposal to remove omeprazole from the NMOP formulary. Patients who currently receive omeprazole from the NMOP would be "grandfathered" so that they could continue to receive omeprazole from the NMOP. Removal of omeprazole from the NMOP formulary would encourage the use of more cost-effective PPIs.

   Committee members and other attendees expressed concern that constraining availability of such a widely used drug could discourage patients from using the NMOP. Others were concerned that patients might simply get omeprazole prescriptions filled at retail pharmacies at a higher cost to the government and the patient. The Committee voted to retain omeprazole on the NMOP formulary.

9. **ANTIBIOTIC PROPHYLAXIS FOR ANTHRAX EXPOSURE** – The Committee discussed the recent memorandum from Health Affairs supporting Centers for Disease Control and Prevention (CDC) guidelines for antibiotics used for prophylaxis for anthrax exposure. They also reviewed data on the number of prescription fills for ciprofloxacin in the Managed Care Support Contractor (MCSC) retail networks, MTFs, and the NMOP. Although there were modest increases in the number of prescription fills for ciprofloxacin in early to mid October, utilization now appears to have returned to pre-September 11th levels. Increased usage was most notable in affected areas (Florida and Washington). The DoD P&T Committee, the PEC, and TMA will use Pharmacy Data Transaction Service (PDTS) data to monitor usage of ciprofloxacin and doxycycline (and other antibiotics that may be used for anthrax prophylaxis in the future) in MTFs, the NMOP, and the retail network.

10. PRIOR AUTHORIZATIONS

A. *Cost avoidance from NMOP prior authorizations (PAs)* – Cost avoidance analyses were not completed for this quarter due to lack of data for September 2001.

B. *Changes to PA criteria for COX-2 inhibitors* – In Oct 2001, celecoxib (Celebrex) 100 mg capsules received a supplemental indication from the Food and Drug Administration (FDA) for the management of acute pain in adults and treatment of primary dysmenorrhea. Existing NMOP PA criteria for COX-2 inhibitors allow use of rofecoxib for 20 days or less in patients with risk factors for GI adverse events, but not celecoxib, which previously lacked any indication for acute use. The Committee decided to table this issue until the next meeting when the following information is expected to be available: new package labeling for celecoxib; the percentage of rofecoxib prescriptions in the NMOP written for short-term use; and actions taken at the Jan 02 meeting of Merck-Medco's internal P&T committee (since the NMOP criteria were adapted from and are similar to criteria used by Merck Medco for other mail order clients).

C. *Clinical Rationale Statements on NMOP PA forms* – There are two versions of the NMOP PA request forms: (1) forms maintained on the PEC website for download by patients and providers, and (2) forms used internally by Merck-Medco to fax to providers when prior authorization is needed. A year ago the DoD P&T Committee decided that NMOP PA request forms should include a clinical rationale statement. The task of constructing the clinical rationale statements was delegated to the PEC staff.

   The PEC staff has encountered significant difficulties in constructing and updating the clinical rationale statements. Space is limited on the single-page forms, so it is difficult to construct complete, coherent clinical rationale statements that will fit on the forms. Any changes in the clinical rationale statements on the forms used by Merck Medco must go through a lengthy approval process.

   The Committee decided to remove the clinical rationale statements from the NMOP PA request forms, but make them available on the PEC website. The NMOP PA forms maintained on the PEC website will contain links to the clinical rationale on the PEC website. The Committee also decided that it would review and approve changes to the clinical rationale statements on the PEC website on an ongoing basis. The Committee reviewed and revised the clinical rationale statements for each of the drugs subject to prior authorization. The information on the PEC website will be updated to reflect these changes.

D. *Combination antifungal therapy for onychomycosis* – Prescription data from one MCSC indicated that only 9 patients received concurrent therapy with ciclopirox and a systemic antifungal during the 21-month time period from Jan 2000 to Sep 2001. The Committee concluded that the incidence of concomitant use is too low to warrant changing PA criteria for the antifungals for onychomycosis.

E. *Status of the PA for sildenafil (Viagra) in the NMOP and retail network* –MAJ Bellemin presented data from the NMOP assessing the potential impact of removing the sildenafil PA. He reported that the cost avoidance attributable to the PA for sildenafil in the NMOP over the 1-year time period April 2000 to March 2001 was about $14.00 per prescription using the same

model routinely used to monitor cost avoidance from the NMOP PA program. He recommended that the PA for sildenafil be continued.

Bill Hudson (Humana) also recommended that the sildenafil PA be continued. He presented data concerning the impact of the prior authorization for sildenafil in the TRICARE regions managed by Humana Military Healthcare Services (HMHS).

HMHS has required prior authorization for sildenafil in Regions 3/4 since mid June of 1998. Upon implementation of the PA requirement, utilization declined from over 1200 prescriptions per month to approximately 200 scripts per month. During 2000 through March 2001, utilization and prior authorization requests leveled off at approximately 500 scripts and 100 requests per month. Upon implementation of the TRICARE Senior Pharmacy program in April 2001, utilization approximately doubled, but the rate of denials remained constant at about 20%.

A distinctly different pattern is seen in Regions 2/5, which did not require prior authorization for sildenafil prior to April 2001. HMHS acquired the contract to manage these regions in June 2001. Sildenafil utilization was two to three times greater in Regions 2/5 than in Regions 3/4, even though the population of Regions 2/5 is about 20% smaller than Regions 3/4. During this time, Regions 3/4 had about 900 fewer claims per month than Regions 2/5 even though only about 30 requests for sildenafil were denied each month. The differences between Regions 3/4 and 2/5 in sildenafil utilization support the existence of a "sentinel effect" due to the presence of the PA program in Regions 3/4.

The PA may also enhance patient safety by assessing whether patients are currently receiving nitrates. The interaction between sildenafil and nitrates is one of the drug interactions most commonly detected by PDTS.

The Committee decided not to change the sildenafil PA in the NMOP or retail network.

11. **CLARIFICATION OF GROWTH HORMONE ON NMOP COVERED INJECTABLES LIST** – The Committee clarified the listing for somatropin, a human growth hormone, on the NMOP Covered Injectables list to include all of the brand names for this product. MAJ Mickey Bellemin confirmed that the NMOP is filling prescriptions for all brands of somatropin.

12. **CLARIFICATION OF HUMAN CHORIONIC GONADOTROPIN (HCG) PRODUCTS ON NMOP COVERED INJECTABLES LIST** – HCG is currently on the NMOP Covered Injectables List as "Human Chorionic Gonadotropin injection." The Committee added the recombinant HCG product Ovidrel (choriogonadotropin alfa) to the NMOP Covered Injectables List.

13. **ACCUTANE QUANTITY LIMIT** – Mark Petruzzi confirmed that the NMOP is complying with new FDA requirements for dispensing of Accutane, including limiting dispensing to a months supply and requiring a new prescription bearing a special sticker (which certifies that female patients have a negative pregnancy test and have received counseling on pregnancy prevention) prior to dispensing each months supply.

14. SUBCOMMITTEE REPORT: PROVISION OF INJECTABLE DRUGS IN THE NMOP OR RETAIL NETWORK PHARMACIES – LtCol (select) George Jones reported on the work of the subcommittee regarding provision of injectable drugs in the NMOP and retail network pharmacies. The subcommittee's goal was to optimize patient access, outcome, and satisfaction balanced with safety and cost efficiency. A guiding principle was that legislation or policy should not take the place of clinical judgment.

The subcommittee analyzed data from PDTS for MTFs, retail network pharmacies, and the NMOP to determine what injectable medications are being filled in each point of service. The subcommittee discussed the trend in the civilian sector to move high cost injectable drugs that were historically provided through provider offices into pharmacy distribution systems in an attempt to attain more control and information about injectable use and decrease costs through volume purchasing strategies.

LtCol (select) Jones commented that the subcommittee had not found any civilian plan that had a usable method of categorizing drugs into those that could be self-administered vs. those that should only be provided through provider offices. Plans differed drastically on what injectable drugs were covered as part of the pharmacy benefit, ranging from insulin and allergy kits only to an extensive list (basically everything except investigational drugs). Many plans have a positive list of drugs that are provided through the pharmacy benefit. Most plans have a system to handle exceptions and special needs. An industry report highlighted one plan that "optimized" distribution of injectables by directing patients to use mail order as their primary source for chronically used injectables.

The subcommittee made preliminary recommendations:

- Continue to provide injectables through the pharmacy benefit in the current manner. No significant misadventures or problems have been reported.
- Expand the number of injectables available through the NMOP. MAJ Bellemin and Mark Petruzzi (Merck-Medco) reported that the subcommittee would review Merck-Medco standard formulary planning list of injectable products as to what is usually covered. The subcommittee will review for next meeting and make specific recommendations. Mark Petruzzi noted that the idea of providing injectables to provider offices is something that Merck Medco is looking at for its commercial clients.
- MTFs continue to meet the needs of their patients through formulary addition or special purchases of injectable products.

15. CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN) – Because of specialized educational requirements mandated by the FDA, dofetilide is only available for outpatient use through Stadtlander's Pharmacy/CVS Procare (which is a non-network pharmacy for DoD beneficiaries). LCDR Ted Briski reported that a plan has been worked out between Pfizer and DSCP to establish a centralized policy and financing procedure that should allow the drug to be obtained for DoD patients at federal pricing and prevent DoD patients from potentially having to pay the copay for a non-network pharmacy. Members commented that more drugs requiring controlled distribution systems are being approved and that similar issues are likely to continue to arise.

16. CONTROLLED DISTRIBUTION OF PEGINTERFERON ALFA 2B (PEG-INTRON; SCHERING) – Schering has instituted a special-distribution process for PEG-Intron due to concerns that unregulated distribution of the product could lead to shortages. Patients must begin the entire course of therapy again if it is interrupted.

Patients using retail network pharmacies or the NMOP will use the same process as Schering's commercial customers. Patients will call 888-437-2608 to self-enroll into the PEG-Intron Access Assurance program and receive an identification number. Patients will supply the identification number to the pharmacy along with their prescription or refill request. The pharmacy will place an order through its usual wholesaler, using the patient's ID number. The wholesaler will ship the product to the pharmacy to arrive within 5 days.

Patients using MTF pharmacies will not have to supply an identification number. MTF pharmacies will input the prescription into CHCS. The PDTS Customer Service Support Center will generate a weekly report of DoD patients newly started on PEG-Intron (using masked patient identifiers) and provide this to the PEG-Intron Access Assurance program. Schering will internally assign an ID number. No order authorization will be required. Schering is in the process of working out details of the program. Schering expects to submit a Memorandum of Understanding to DoD for approval before the end of the year.

17. ADJOURNMENT – The meeting adjourned at 1200 hours. The next meeting will be held at the Non-Commissioned Officers Club, Fort Sam Houston, TX starting at 0800 on Wednesday, 13 February 2002. All agenda items should be submitted to the co-chairs no later than 11 January 2002.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Cefditoren pivoxil tablets (Spectracef; TAP)	29 Aug 01; third generation cephalosporin for treatment of acute exacerbations of chronic bronchitis, pharyngitis, tonsillitis, and uncomplicated skin and skin structure infections	Added to the NMOP Formulary	**Quantity Limits** 10 days supply (40 tabs) per 30 days in NMOP and retail network **Rationale for Quantity Limits:** Spectracef is **only** indicated for acute therapy. Pivalate-containing compounds have caused clinical carnitine deficiency when used over a period of months. The effect of repeat short-term courses on carnitine levels is unknown. **Prior Authorization:** No	Not added to the BCF **Similar BCF Drugs:** Amoxicillin/ clavulanic acid oral; cephalexin oral (first generation cephalosporin)
Darbepoetin alfa for injection (Aranesp; Amgen)	17 Sep 01; erythropoietin analog for treating the anemia of chronic renal failure in dialysis and non-dialysis patients; administered every 1-2 weeks by IV or SQ injection	Added to the NMOP Formulary **Note**: Erythropoietin products (Epogen, Procrit) are currently on NMOP Covered Injectables List; darbepoetin alfa may be self-administered	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **Similar BCF Drugs:** none
Tramadol + acetaminophen tablets (Ultracet; Johnson & Johnson)	15 Aug 01; short-term (5 days or less) management of acute pain	Added to the NMOP Formulary **Note**: Although Ultracet is only indicated for short-term management of acute pain, both tramadol and acetaminophen are used on a longer-term basis; in addition, excluding the product from the NMOP Formulary would further delay therapy in the unlikely event that patients submit prescriptions for short-term therapy to the NMOP.	**Quantity Limits** 240 tablets per 30 days, 720 tablets per 90 days **Rationale for Quantity Limits:** Maximum daily quantity established by labeling as 8 tabs per day; consistent with existing quantity limits for tramadol **Prior Authorization** No	Not added to the BCF **Similar BCF Drugs:** multiple analgesics; tramadol is not on the BCF
Mixed salts of a single-entity amphetamine product, immediate/ delayed release (Adderall XR; Shire)	18 Oct 01; once daily treatment of attention deficit/hyperactivity disorder	Added to the NMOP Formulary	**Quantity Limits** NMOP: General rule for Schedule II controlled substances for treatment of ADHD applies (90 days supply; no refills) **Prior Authorization** No	Not added to the BCF **Similar BCF Drugs:** Methylphenidate oral (includes Concerta, but does not include Metadate CD)

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP and/or retail network formulary restrictions**	**BCF Status**
Ribavirin capsules (Rebetol; Schering-Plough)	26 July 01; anti-viral nucleoside analog capsules previously only available as a component of the combination product Rebetron, now available as a separate product indicated for combination use with interferon alfa 2b (Intron A) in chronic hepatitis C	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **Similar BCF Drugs:** none
Albuterol solution for inhalation - 0.63 mg/3 mL, 1.25 mg/3 mL (AccuNeb; Dey)	01 May 01; pre-mixed, pre-measured reduced dosages of albuterol inhalation solution for children with asthma aged 2-12	Already included on NMOP Formulary as new formulation of existing product	**Quantity Limits** 8 boxes of 25 per 30 days (200 unit doses); 22 boxes of 25 per 90 days (550 unit doses) **Rationale for Quantity Limits:** Consistent with existing quantity limits for nebulization solutions; sufficient to provide 6 treatments per day **Prior Authorization** No	Current BCF listing for albuterol solution for inhalation clarified to not include AccuNeb **Similar BCF Drugs:** albuterol solution for inhalation; albuterol oral inhaler
Comments about AccuNeb: The Council voted to exclude the new concentrations from the existing BCF listing for albuterol solution for inhalation because it seems doubtful that the incremental benefit will exceed the incremental cost. The Council also had concerns about the potential for medication errors (underdosing) if all MTFs are required to have all three strengths on their formularies. Council members noted that because the lower vital capacity of pediatric patients decreases total drug exposure, overdosing is not typically a problem with nebulized albuterol. If lower concentrations are desired, these may be easily attained with existing products.				
Amoxicillin/ Clavulanate Potassium Powder for Oral Suspension (Augmentin ES-600; Glaxo SmithKline)	22 Jun 01; Pediatric suspension of amoxicillin/clavulanate with double the previous concentration of amoxicillin, same clavulanate concentration; indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media.	Already included on NMOP Formulary as new formulation of existing product	**Quantity Limits** General rule applies **Prior Authorization** No	Current BCF listing for amoxicillin/ clavulanic acid oral will include this new formulation **Similar BCF Drugs:** amoxicillin/ clavulanic acid oral
Comments about Augmentin ES-600: The Council noted that the cost per course of therapy with Augmentin ES-600 oral suspension appears to be comparable to giving standard concentration Augmentin plus an dose of amoxicillin suspension to provide the same amounts of amoxicillin and clavulanic acid. Other oral dosage forms with double concentrations of amoxicillin are already available and are also included in the BCF listing for amoxicillin clavulanic acid oral.				
Tenofovir disoproxil fumarate (Viread; Gilead Sciences)	26 Oct 01; in combination with other antiretroviral medications for the treatment of HIV infection	Already included on NMOP Formulary following precedent for HIV drugs. Confirmed by the Committee	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **Similar BCF Drugs:** None

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**
   A. *Additions to the BCF*
      1) Tretinoin cream, 0.025% and 0.05% [excludes products only indicated for wrinkles (e.g., Renova)]
      2) Diazepam 5 mg oral tablets
      3) Clonazepam 0.5 mg oral tablets
   B. *Deletions from the BCF*
      1) Cromolyn sodium oral inhaler
      2) Cromolyn sodium solution for inhalation
      3) Haloperidol oral
   C. *Changes and clarifications to the BCF*
      1) The current BCF listing for albuterol solution for inhalation was clarified to exclude the 0.63-mg/3 mL and 1.25 mg/3 mL strengths (AccuNeb)
      2) The current BCF listing for amoxicillin/clavulanic acid oral will include Augmentin ES-600 oral suspension
2. **NMOP FORMULARY CHANGES**
   A. *Additions to the NMOP Formulary* (See Appendix A for details)
      1) Rabeprazole oral (interim decision effective 1 Oct 2001)
      2) Pantoprazole oral (interim decision effective 1 Oct 2001)
      3) Lansoprazole oral (as of 15 Nov 2001)
      4) Choriogonadotropin alfa (Ovidrel) for injection – added to NMOP Covered Injectables List
      5) Ceftidoren pivoxil tablets (Spectracef; TAP) – quantity limits apply, see below
      6) Darbepoetin alfa for injection (Aranesp; Amgen) – added to NMOP Covered Injectables List
      7) Tramadol/acetaminophen 37.5 / 325 mg tablets (Ultracet; Johnson & Johnson) – quantity limits apply, see below
      8) Mixed salts of a single-entity amphetamine product, immediate/delayed release (Adderall XR; Shire)
      9) Ribavirin capsules (Rebetol; Schering-Plough)
      10) Tenofovir disoproxil fumarate (Viread; Gilead Sciences)
   B. *Exclusions from the NMOP Formulary*
      1) Lansoprazole oral (interim decision effective 1 Oct 2001; lansoprazole was added to the NMOP Formulary as of 15 Nov 2001)
      2) Esomeprazole oral (interim decision effective 1 Oct 2001; esomeprazole remains excluded from NMOP Formulary)

C. Clarifications to the NMOP Formulary

1) Listing for somatropin (human growth hormone) on NMOP Covered Injectable List clarified to list all of the brand names for this product

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**

A. Quantity limit for cefditoren pivoxil tablets: 10 days supply (40 tablets) per 30 days in NMOP and retail network

B. Quantity limit for tramadol/acetaminophen 37.5/325 mg tablets: 240 tablets per 30 days; 720 tablets per 90 days

C. Albuterol solution for inhalation – 0.63 mg/3 mL, 1.25 mg/3 mL: 8 boxes of 25 per 30 days (200 unit doses); 22 boxes of 25 per 90 days (550 unit doses)

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)** – None

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MCCS-GPE **14 November 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 14 November 2001 at the Uniformed Services University of the Health Sciences. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL Mike Heath, MS (representing MAJ Brett Kelly)	Army
COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army
CAPT Chuck Bruner	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board

MEMBERS ABSENT

Dick Rooney	Department of Veterans Affairs

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
COL Ardis Meier, BSC	Air Force Pharmacy Consultant
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LTC Deborah Bostock, MC	Air Force
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Maria Ionescu	Pharmacy Benefits Division, TMA
MAJ Barb Roach, MC (by teleconference)	DoD Pharmacoeconomic Center
Howard Altschwager	Deputy General Counsel, TMA
Dave Bretzke	DoD Pharmacoeconomic Center
Michael McGregory	Pharmacy Student, Butler University Pharm.D. Program
Shirif Mitry	Pharmacy Student, TMA
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES

The Council approved the minutes of the last meeting with two corrections:

- The reference to seborrheic keratoses on Page 15 of the Aug 01 DoD P&T Executive Council minutes was changed to actinic keratoses.
- The prescription data in Table 2 on Page 3 of the Aug 01 DoD P&T Executive Council minutes are incorrect. The corrected table is shown below:

Table 2: Prescription fills for COX-2 Inhibitors and Traditional NSAIDs in the MHS, July 2001

	MTF prescriptions	MCSC retail network prescriptions	NMOP prescriptions	Total
COX-2 inhibitors	45,201 (15%)	40,106 (59%)	12,824 (74%)	98,131 (26%)
Traditional NSAIDs	252,134 (85%)	27,857 (41%)	4,480 (26%)	284,471 (74%)
Total	297,335	67,963	17,304	382,602

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4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

According to prime vendor data, Military Treatment Facilities (MTFs) spent $46.5 million on AMP drugs in FY 2001. Prime vendor data are incomplete for 44 MTFs in the second half of FY 01, so MTFs actually spent more than $46.5 million on AMP drugs during FY 01.

5. SUBCOMMITTEE REPORT: OBTAINING INPUT FROM PROVIDERS

COL Downs reported how the VA uses the Medical Advisory Panel (MAP) and the regionally based formulary management process in the 22 Veterans Integrated Service Networks (VISNs) to systematically obtain input from providers on formulary and contracting issues. The Council noted that most TRICARE regions have not established a regional formulary management process. LCDR Briski reported a lack of consensus among pharmacy officers regarding methods to obtain prescriber input. Some pharmacy officers favor communicating through lead agents, while others favor military service lines of communication.

LtCol (select) George Jones noted that actions of the DoD P&T Committee are a standing agenda item for his local P&T committee, which prompts input and communication. He suggested that MTF P&T Committees should routinely include DoD P&T Committee actions on their meeting agendas. He also noted that the PEC website provides access to DoD P&T Committee documents. (The PEC website is available at www.pec.ha.osd.mil.)

The Council decided to obtain prescriber input primarily by having the PEC communicate with the chairs of MTF and/or regional P&T committees and MTF pharmacy chiefs. The Council did not reach a definitive conclusion regarding the process that will be used to accomplish this type of communication. However, there was support voiced for including lead agent pharmacists and medical directors as integral parts of the process. The PEC agreed to present various process options at the next meeting.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

A. *Contract awards, renewals, and terminations*

- As of November 2001, 54 joint VA/DoD and 3 DoD-only contracts for drugs or pharmaceutical supplies are in effect. A joint VA/DoD returned goods contract is also in effect. Information on national pharmaceutical contracts, including NDC numbers and prices, is available on the DSCP website (www.dmmonline.com).
- Contracts for terazosin, acyclovir, hydroxyurea, pentoxifylline, rifampin, sucralfate, nortriptyline, prazosin, diltiazem XR, ranitidine, insulin, verapamil, and albuterol inhalers were renewed.
- The cimetidine contract was extended until May 02.
- Contracts for cerivastatin, amoxicillin, azathioprine, and omeprazole were cancelled.
- New contracts were awarded for cyclobenzaprine tablets, isosorbide dinitrate tablets, loperamide capsules, methocarbamol tablets, verapamil immediate release tablets, and lactulose syrup.

B. *Financial impact of contracts* – COL Remund reported on the percent reduction in cost per unit for drugs covered by national pharmaceutical contracts (see Table 1).

Table 1: Percent Reduction in Cost per Unit for Drugs Covered by National Pharmaceutical Contracts*

Drug/Drug Class	% Reduction
Diltiazem extended release	48%
Lisinopril	45%
PPIs	36%
Non-sedating antihistamines	36%
Statins	31%
All contracts	33%

*From start dates of contracts to 30 Sep 2001

C. *Status of Contracting Initiative for Leutinizing Hormone Releasing Hormone (LHRH) agonists* – CAPT Torkildson reported that the joint VA/DoD contracting action to select a LHRH agonist for the Basic Core Formulary (BCF) (for the treatment of prostate cancer only) is awaiting completion of updates to the VA clinical review. The VA extended its contract for Zoladex until early 2002 in preparation for a joint VA/DoD contracting initiative. The DoD Blanket Purchase Agreements (BPAs) for Lupron and Zoladex remain in place. The BPA for Zoladex has been modified since the last meeting to remove the market share requirement and to extend the expiration date of the BPA until 30 April 2002. The Lupron BPA has also been modified to maintain the current price until 30 April 2002.

D. *Non-sedating antihistamine contract* – The market share for fexofenadine (as a percent of all prescriptions for non-sedating antihistamines dispensed at MTF pharmacies) increased from 50% prior to the contract to approximately 89% by the end of October 2001. The prescription market shares for fexofenadine and loratadine continue to remain stable in the retail pharmacy networks and the National Mail Order Pharmacy (NMOP), indicating that MTFs are maximizing the use of fexofenadine without shifting loratadine prescriptions into the retail pharmacy network or NMOP. The average cost per non-sedating antihistamine tablet/capsule purchased by MTFs dropped by 36%, from $0.87 (pre-contract) to $0.56 (as of Sep 2001).

E. *Statin Contract* – The Council considered two options regarding the renewal of the simvastatin contract:

Option 1: Renew the simvastatin contract for the final option year (February 2002 to February 2003). The statin class remains "closed" on the BCF. Simvastatin is the only statin on MTF and NMOP formularies.

Option 2: Do not renew the simvastatin contract. The statin class would be "open" on the BCF. MTFs may have additional statins on formulary. DoD P&T Committee decides which statins are on the NMOP formulary.

The Council assessed the relative safety/tolerability of statins; effectiveness in reducing LDL-cholesterol; evidence of effect on cardiovascular morbidity and mortality; ability of simvastatin to meet the clinical needs of the DoD beneficiary population; current statin

costs; likelihood of future price reductions for simvastatin, input from providers; and potential collaboration with the VA on the statin class in the future.

The Council concluded that:

- Simvastatin has a well-established safety and tolerability profile.
- Simvastatin is proven to reduce cardiovascular morbidity and mortality.
- Simvastatin is currently used by > 95% of statin patients at MTFs.
- Non-contracted statins can be provided through the special order process for patients who need them.
- Simvastatin is more cost-effective than other statins in treating patients to LDL goal.
- The cost per dose of statin therapy has decreased by 31% at MTF pharmacies in the first two years of the statin contract. Additional reductions in the cost per dose are more likely to occur if the contract is renewed than if it is not renewed.
- The VA strategy for managing statins is linked to renewal of the DoD statin contract.
- Contract renewal will facilitate joint management of statins by DoD and VA.

The Council decided to advise DSCP to renew the contract for simvastatin.

F. *Status of contracting initiative for nasal corticosteroid inhalers* –The Council reviewed an updated analysis of aqueous nasal corticosteroid dosing frequency and input from providers to assess whether or not flunisolide should be included in a solicitation for a closed class contract.

- An analysis of MTF prescription data from Jun 00 to May 01 showed the following percentages of patients who were treated with a single daily dose of an aqueous nasal corticosteroid:

fluticasone	93.7%
mometasone	93.7%
beclomethasone 84mcg	91.9%
triamcinolone	85.5%
budesonide	60.0%
flunisolide	27.2%

- DoD providers report a higher rate of burning and stinging with flunisolide than with other nasal corticosteroid products.

The Council concluded that flunisolide should not be included in the solicitation because it is dosed more than once daily much more frequently than other products and because providers have reported tolerability problems. The Council concluded that budesonide should not be included in the solicitation because it is dosed more than once daily much more frequently than other products. The Council also recommended that:

- The contract should not apply to use of aqueous nasal steroids in patients under 6 years of age. While it is not known whether the nasal corticosteroids differ significantly in their potential to affect the growth and development of pediatric patients, the Council prefers to allow MTFs to select an alternate agent for this patient

population if they so desire. The PEC estimates that less than 4% of all aqueous nasal steroid inhaler prescriptions are for patients who are under 6 years of age, so exclusion of this patient population will not have a negative impact on the contract.

- The contract should specify that all new patient starts must use the contracted agent, but should not dictate that existing patients be switched to the contracted agent.

The Council reiterated its support for a joint VA/DoD solicitation if agreement can be reached on the products that are included in the solicitation. If agreement cannot be reached, the Council recommends that DoD pursue its own contract.

G. *Potential contracting initiative for carbamazepine* – Multiple AB-rated generic products are available for commonly used strengths of carbamazepine. MTF usage of carbamazepine has declined about 20% over the past two years to a current usage rate of 700,000 tablets/month. MTFs spent about $1.5 million on carbamazepine during FY 01 ($1.4 million for the brand name product (Tegretol) and $0.1 million for generic products). The average cost is currently $0.22/tablet for Tegretol and $0.05/tablet for generic carbamazepine.

Generic versions of carbamazepine currently account for about 20% of total carbamazepine usage at MTFs (up from 5% two years ago). In light of the large cost difference between the brand and generic versions of carbamazepine, the Council asked the PEC to investigate why the usage of the brand name drug continues to predominate at MTFs.

H. *Potential contracting initiative for triptans* – In the absence of information that negates concerns about variability in patient response, the Council is unwilling to support a closed class contract for a single oral triptan. The Council asked the PEC to continue to explore potential contracting initiatives for this drug class.

I. *Potential contracting initiative for angiotensin receptor blockers (ARBs)* – MTF utilization and expenditures for the ARBs are rising, and clinical information concerning these agents is evolving. The PEC is collaborating with the VA Pharmacy Benefits Management Strategic Healthcare Group (VA PBM) on a class review of the ARBs. The Council asked the PEC to continue to work with the VA to complete the class review and explore the feasibility of contracting initiatives in this drug class.

J. *Contracting initiative for fluoroquinolones* – Independent class reviews completed by the VA PBM and the PEC concluded that gatifloxacin (Tequin) and levofloxacin (Levaquin) offer advantages over the other fluoroquinolones in safety and tolerability (side effect and drug interaction profiles), expanded gram-positive spectrum of activity, and once daily dosing. Both reviews concluded that levofloxacin and gatifloxacin are the only two fluoroquinolones that are therapeutically interchangeable and clinically acceptable as a "workhorse" oral fluoroquinolone. Levofloxacin is currently on the BCF in accordance with a BPA.

Ciprofloxacin is dosed twice daily, has poor coverage for *S. pneumoniae*, and has several clinically significant drug interactions. The Council concluded that ciprofloxacin is not therapeutically interchangeable with gatifloxacin or levofloxacin. The Council noted that

ciprofloxacin is the only fluoroquinolone currently approved for post-exposure prophylaxis of anthrax, but the proposed contract initiative would not affect the availability of usage of ciprofloxacin for anthrax exposures.

The DoD P&T Executive Council agreed to support a contracting initiative to choose a workhorse oral fluoroquinolone for the BCF.

7. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove cromolyn sodium oral inhaler and solution for inhalation from the BCF* –An Army pharmacist provided the following rationale for the request:

> Cromolyn is relatively infrequently used in clinical practice. Cromolyn is a weak anti-inflammatory agent and is rarely prescribed. Inhaled steroids are used almost exclusively for this indication and are now acceptable in patients <2years of age with use of a spacer mask.

The mast cell stabilizers (cromolyn and nedocromil) produce only minor side effects (nasal congestion, cough, sneezing, dry throat). Nedocromil has an unpleasant taste. Mild-persistent asthma can be controlled with cromolyn in approximately 60 to 75% of patients, but 4 to 6 weeks of usage four times a day may be needed to attain maximum benefit. The mast cell stabilizers are not as effective as the inhaled corticosteroids, which are the agents of choice for long-term control of persistent asthma.

The PEC requested provider input on this issue and received 129 responses: 70 favoring removal from the BCF; 42 against removal from the BCF; 13 unsure; and 4 wanted to remove the MDI, but keep the nebulizer solution. Providers made several key points:

- Keeping cromolyn on the BCF may promote less effective, outdated therapy. Removing it from the BCF may encourage providers to more appropriately treat persistent asthma with inhaled corticosteroids.
- Despite parental concerns, studies reporting growth reduction with inhaled corticosteroids do not offer sufficient justification for avoiding the use of inhaled corticosteroids in children with asthma.
- Data suggest that delays in initiating maintenance therapy with inhaled corticosteroids result in less recovery of lung function in children with asthma.
- The best evidence for use of cromolyn is for people whose asthma symptoms are solely induced by exercise and who do not tolerate a long-acting beta agonist like salmeterol.

Prescriptions for cromolyn MDIs at MTFs declined by 52% over the past year, from 3265 prescriptions in Sep 2000 to 1562 prescriptions in Sep 2001. Prescriptions for cromolyn nebulizer solution declined by 55%, from 957 Rxs in Sep 2000 to 434 in Sep 2001.

The Council removed cromolyn sodium oral inhaler and solution for inhalation from the BCF. MTFs can decide whether or not to keep either or both products on their local formularies.

B. *Request to remove oral haloperidol from the BCF* – An Army pharmacist based this request on the relatively infrequent usage of haloperidol at his MTF.

Haloperidol is a potent antipsychotic with a high propensity to cause adverse effects. MTFs currently fill about 500 haloperidol prescriptions per month. Newer agents such as risperidone, olanzapine, and quetiapine are used more frequently than haloperidol. Primary care providers in the outpatient setting do not commonly prescribe antipsychotics. The Council removed oral haloperidol from the BCF. MTFs can decide whether or not to keep oral haloperidol on their local formularies.

C. *Request to add a no to extremely low androgen oral contraceptive to the BCF* – An Army pharmacist originally requested the addition of Desogen, a monophasic oral contraceptive (OCP) to the BCF. The request was subsequently clarified to be for the addition of a "3rd generation" monophasic OCP classified as having no to low androgenic side effects and 35 mcg of ethinyl estradiol. These OCPs contain the progestin desogestrel (Desogen, Ortho-Cept, Apri) or norgestimate (Ortho-Cyclen).

The purported advantages of OCPs with no to low androgenic effects are lower incidences of weight gain, edema, bloating hirsutism and acne. MAJ Barb Roach reported that she could not find empirical evidence that OCPs differ significantly in androgenic side effects. Head-to-head trials are not available. Most reviewers acknowledge that there is no evidence of significant differences in side effects or efficacy for any of the OCPs, regardless of the progestin contained in the pill or their classification as mono-, bi-, tri-, or estro-phasic products. However, the same reviewers then go on to discuss differences in androgenic side effects with different progestins (apparently based primarily on *in vitro* characteristics of the progestins). A number of providers commented on the propensity for misconception in this therapeutic category.

All OCPs are associated with an increased risk of venous thromboembolism. Some studies suggest an increased potential for venous thromboembolism with the 3rd generation OCPs compared to other OCPs, but the evidence is inconclusive.

The 3rd generation OCPs cost from $10.20 to $15.28 per cycle—much more than most other OCPs. The Council decided not to add a 3rd generation OCP to the BCF because there is insufficient evidence that an incremental clinical benefit exists that would justify the incremental cost.

8. FORMULARY STATUS OF TRETINOIN

Tretinoin cream is indicated for the treatment of acne, and is also commonly used for the treatment of various skin cancers, precancerous conditions (e.g., actinic keratoses), and other dermatological conditions. Tretinoin products are also used for cosmetic treatment of photoaged skin (wrinkles and liver spots). One brand of tretinoin cream, Renova, is specifically indicated for mitigation of fine wrinkles, mottled hyperpigmentation and tactile skin roughness in patients who use comprehensive skin care and sunlight avoidance programs.

Topical retinoids are first line agents for acne. More than 95% of MTFs already have tretinoin cream on formulary. The Council decided to add tretinoin cream 0.025% and 0.05% to the BCF, but excluded products specifically indicated for wrinkles only (e.g., Renova). The Council noted that MTFs may adopt guidelines or retain existing guidelines designed to prevent usage of tretinoin products for cosmetic treatment of photoaged skin.

The NMOP statement of work does not allow tretinoin prescriptions to be filled for patients over the age of 35. The rule exists only in the NMOP statement of work—not in the Code of Federal Regulations or TRICARE policy. PDTS data show that tretinoin prescriptions are routinely filled in MTF and retail pharmacies for patients over the age of 35. The Council considered a proposal to remove the NMOP age restriction so that tretinoin would be more uniformly available to patients across all points of service. Some attendees expressed concern about taking an action that would require modification of the NMOP contract. After extensive discussion, the vote to remove the NMOP age restriction on tretinoin ended in a tie. The age restrictions on tretinoin remain in the NMOP. .

9. REVIEW OF ANXIOLYTICS FOR THE BCF

CAPT Torkildson reported on the PEC review of drugs for the treatment of anxiety disorders: generalized anxiety disorder (GAD), panic disorder/agoraphobia, acute/post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), specific phobia, and social phobia. These six conditions share a common dimension of poor response to stress leading to frequent and intense episodes of negative affect. This dimension is shared with depressive disorders, and is primarily responsible for the observed comorbidity among the anxiety disorders and between these disorders and depression. Each disorder also contains a unique component that distinguishes it from the others, with the possible exception of GAD.

Pharmacotherapy for anxiety disorders includes serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs) and venlafaxine]; benzodiazepines; buspirone; tricyclic antidepressants (TCAs); imipramine; clomipramine; trazodone; and nefazodone. Of these, buspirone, imipramine, trazodone, and four SSRIs are on the BCF.

Serotonin Reuptake Inhibitors – This classification includes the SSRIs and venlafaxine. There is growing support for using this group of drugs as first line therapy for many of the anxiety disorders. SSRIs are now considered the treatment of choice for panic disorder and post-traumatic stress disorder, and as first choice in conjunction with psychotherapy for OCD, specific phobia, and social phobia. Usage of SSRIs for treatment of GAD is increasing. Despite differences in FDA-approved indications, the SSRIs appear similar in safety and efficacy for these conditions. There are already four SSRIs (citalopram, fluoxetine, paroxetine, sertraline) on the BCF.

Venlafaxine inhibits both serotonin and norepinephrine reuptake (similar to TCAs). It was approved by the FDA for depression in 1993, and for GAD in 1999. It has been shown to be effective for GAD with and without coexisting depression. Venlafaxine appears to have a rapid onset of action with a safety profile similar to the SSRIs. Venlafaxine appears to be less costly on a cost per day basis than fluoxetine, paroxetine, or sertraline. It is currently on approximately 88% of MTF formularies, but it is not on the BCF.

The Council decided not to change the SSRIs on the BCF, but instructed the PEC to investigate the potential for addition of venlafaxine extended-release to the BCF as a cost-effective alternative to the SSRIs for the treatment of anxiety disorders.

Benzodiazepines – Benzodiazepines are effective in treating anxiety disorders, including GAD, panic disorder, and social anxiety disorder. The long-term use of benzodiazepines for anxiety disorders is controversial. All benzodiazepines share a risk of sedation, motor vehicle accidents, industrial accidents, and dependence. Rebound anxiety occurs in approximately 15% of patients upon discontinuation. The benzodiazepines are Pregnancy Category D due to the risk of cleft lip/palate. There are currently no benzodiazepines on the BCF.

All benzodiazepines used for treatment of anxiety disorders are available as generics. All strengths of these benzodiazepines are available for less than $0.10 per tablet or capsule. As Schedule IV medications, the administrative burden associated with stocking and record keeping must be considered in adding any of them to the BCF.

Psychiatrists identified clonazepam as a drug that should be considered for the BCF because of a lower abuse potential and more utility in other conditions (e.g., some seizure disorders). Almost all MTFs (99%) are filling prescriptions for the 0.5 mg strength of clonazepam. Some MTFs appear to carry only the 0.5 mg strength.

According to the PEC Formulary database, 100% of facilities have diazepam on their local formulary. About 97% of prescriptions for oral diazepam tablets are for the 5 mg strength.

The Council decided to add clonazepam 0.5 mg and diazepam 5 mg to the BCF. MTFs may have other strengths or formulations of these medications on their formularies.

Buspirone – The utility of buspirone is limited primarily to treatment of GAD. Buspirone has a superior safety profile compared to the benzodiazepines, but a significantly slower onset of action. Many think buspirone is less efficacious than other agents, but under-dosing might be the problem. Buspirone is already on the BCF and MTF pharmacies dispensed nearly 6 million tablets in the first 9 months of FY 01. The Council agreed that buspirone should remain on the BCF.

Tricyclic Antidepressants – Imipramine is useful primarily in GAD. Clomipramine is used to treat OCD. The usefulness of these agents is limited by their side effect profile and potential for accidental or deliberate overdose. SSRIs are equally efficacious, safer, and much better tolerated. Imipramine is already on the BCF. There is no provider support for the addition of clomipramine. The Council made no changes in this drug class.

Trazodone – Trazodone is a heterocyclic antidepressant. Anxiolytic use has been confined primarily to GAD. Although trazodone has no significant safety, tolerability, or efficacy advantages over other active agents, it is relatively inexpensive. Trazodone also has some utility in treating insomnia resulting from SSRI therapy. Trazodone is already on the BCF. The Council made no change to the formulary status of trazodone.

Nefazodone – Nefazodone is an antidepressant with a unique mechanism of action. It was FDA-approved in 1994 for treatment of depression, but is used off-label to treat panic disorder, PTSD, and social phobia. The major advantage of nefazodone is its somewhat superior safety profile, but the daily cost per day of therapy is $1.06 to $3.18. Nefazodone is not on the BCF. Providers expressed no interest in the addition of nefazodone to the BCF and usage in the Military Health System (MHS) is relatively low. The Council made no change in the formulary status of nefazodone.

10. EVALUATION OF THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS (CURE) TRIAL

The CURE trial randomized approximately 12,500 patients (500 patients in the U.S. arm) with unstable angina and non-ST-segment elevation myocardial infarction (MI) presenting within 24 hours of symptom onset to clopidogrel (300 mg load, followed by 75 mg daily, plus aspirin in doses ranging from 75 to 325 mg daily) or aspirin plus placebo. Patients were treated for 3 to 12 months (average of 9 months).

The primary composite outcome of non-fatal MI, stroke, or death due to cardiovascular causes occurred in 9.3% of patients receiving clopidogrel plus aspirin compared to 11.4% of patients receiving aspirin plus placebo. This equates to a relative risk of 0.80 (95% CI 0.72-0.90, $p<0.001$), or a 20% relative risk reduction. The absolute risk reduction was 2.1%, which yields a number needed to treat of 47. The addition of clopidogrel to aspirin appeared to provide both an early (within 2 hours) and sustained benefit.

If 100 patients analogous to those obtaining benefit in the CURE trial were treated for a 9 month period with clopidogrel plus aspirin and a similar group of 100 patients were treated with aspirin only, drug costs for the clopidogrel plus aspirin group would be about $50,220 ($1.86 per patient per day) compared to about $270 ($0.01 per patient per day) for the aspirin only group. Given outcomes of the CURE trial, 9 patients (9.3%) in the clopidogrel plus aspirin group and 11 (11.4%) in the aspirin only group would be expected to experience the primary outcome of non-fatal MI, stroke, or death. Dividing the incremental cost of clopidogrel therapy ($50,220 - $270) by the number of averted events (2) results in an incremental cost of $25,000 per averted event.

The increased risk of bleeding in the clopidogrel plus aspirin group must also be considered. During the CURE trial, a significantly higher percentage of patients receiving clopidogrel plus aspirin experienced major bleeding compared to those receiving aspirin plus placebo (3.7% vs 2.7%, $p = 0.001$), a number needed to harm of 100. Thus, for every 100 patients treated with clopidogrel plus aspirin, one additional patient would be expected to have a major bleed compared to 100 patients receiving aspirin alone (or one major bleed per two events averted). Combination therapy also resulted in a significantly higher percentage of patients experiencing non-life threatening bleeding, minor bleeding, and bleeding requiring transfusion of $\geq$ 2 units of blood. The percentage of fatal bleeding episodes was 2.2% for clopidogrel plus aspirin compared to 1.8% with aspirin plus placebo (a statistically non-significant difference).

The definitions used in the CURE trial for the various types of bleeding differ from widely accepted definitions used in the ACCP Consensus Conference on Antithrombotic Therapy guidelines published each year in CHEST (the “CHEST guidelines”) and the “Thrombolysis in Myocardial Infarction” (TIMI) trials. The variance in bleeding definitions raises the

concern that the risk of bleeding among patients receiving clopidogrel plus aspirin may have been even larger if the bleeding definitions in the CHEST guidelines and TIMI trials had been used.

The Council decided not to add clopidogrel to the BCF. The Council asked the PEC to request additional information from the manufacturer about the incidence of bleeding found in the CURE trial—ideally information about the bleeding rates using the definitions found in the CHEST guidelines and TIMI trials.

11. PROTON PUMP INHIBITORS

COL Remund reported on a significant shift in proton pump inhibitor (PPI) prescription market shares after omeprazole (Prilosec) was removed and rabeprazole (Aciphex) was added to the BCF on 1 October 2001. By the first week in November, rabeprazole accounted for 54% of MTF PPI prescription fills. The rapid switch to rabeprazole by MTF pharmacies essentially negated the effect of the huge increase in the price of omeprazole. The weighted average cost per unit for PPIs increased significantly during the first part of October, but trended back down to $1.08 per unit by the first week in November (just under the $1.09 cost per unit that existed prior to termination of the omeprazole contract).

12. COX-2 INHIBITORS

MTF prescription fills and expenditures for the COX-2 selective inhibitors (celecoxib and rofecoxib) leveled off over the past six months. Council members speculated that uncertainty about cardiovascular safety and the ability of these agents to significantly reduce the risk of GI events (especially in patients taking aspirin for cardiac prophylaxis) may have played a role.

13. ADJOURNMENT

The meeting adjourned at 1600 hours on 14 Nov 2001. The next meeting will be held at the Non-Commissioned Officers Club, Fort Sam Houston, TX starting at 0800 on 12 Feb 2002. All agenda items should be submitted to the co-chairs no later than 11 Jan 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

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MCCS-GPE **16 AUGUST 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0800 hours on 16 August 2001, at the Non-Commissioned Officers Club, Ft. Sam Houston, TX.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
CAPT Robert Rist	Coast Guard
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
William Hudson	Humana, Inc
Gene Lakey	TriWest
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)

MEMBERS ABSENT

COL Rosa Stith, MC	Army
Dick Rooney	Department of Veterans Affairs
Ray Nan Berry	Health Net Federal Services
Ron McDonald	Sierra Military Health Services

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Gary Blamire, MSC	Lead Agent Office, Region 6
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
Capt Andrew Meadows, BSC	Baylor University Resident
SFC Augustin Serrano	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
David Chicoine	Uniformed Services Family Health Plan
Eugene Moore	DoD Pharmacoeconomic Center
Mark Petruzzi	Merck-Medco
Carol Scott	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
Gina Wu	Merck-Medco

3. **REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES** – The minutes from the last meeting erroneously listed Shannon Rogers as an employee of Merck-Medco. Ms. Rogers is an employee of Humana.

4. **UNIFORM FORMULARY**– COL Davies reported that a draft of the Uniform Formulary regulation is being staffed in TMA.

5. BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES – The Committee determined the NMOP formulary status, NMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for the 6 new drugs listed below. See Appendix A for more information.

- Almotriptan 6.25- and 12.5-mg tablets (Axert; Pharmacia & Upjohn)
- Drospirenone 0.3 mg / ethinyl estradiol 30 mcg tablets (Yasmin; Berlex);
- Desogestrel/ethinyl estradiol tablet (Cyclessa; Organon)
- Valganciclovir tablets (Valcyte; Syntex)
- Albuterol sulfate 3 mg and ipratropium bromide 0.5 mg per 3 mL (DuoNeb Solution for Inhalation; Dey Labs)
- Insulin aspart injection (NovoLog; Novo Nordisk)

6. USAGE PATTERNS OF DRUGS FORMERLY ON NMOP PREFERRED DRUG PROGRAM – On 1 April 2001, Merck-Medco (the NMOP contractor) ceased making calls to physicians concerning all non-preferred/preferred drug pairs in the NMOP Preferred Drug Program except diltiazem. The committee was interested in seeing how discontinuation of the preferred drug program affected usage patterns of these drugs. Oxybutynin immediate release and Adalat CC experienced the largest drop in market share versus the non-preferred products. The market share changes for ranitidine, acyclovir, and generic NSAIDs were much smaller. Except for the antiviral drugs (acyclovir, famciclovir, valacyclovir), all the products experienced sharp increases in prescription volume because of the implementation of the TRICARE Senior Pharmacy Program.

7. PRIOR AUTHORIZATIONS

A. *Temporary lapse in the NMOP Prior Authorization Program* – Prior authorizations in the NMOP were temporarily suspended in April and early May due to sharp increases in workload associated with the expansion of the pharmacy benefit to all beneficiaries over 65 years of age. Table 1 shows when specific PAs were "turned off" in the NMOP. Initial implementation of the PA for ciclopirox topical solution (Penlac) was delayed to 10 May 2001.

Table 1: Temporary suspension of NMOP PAs due to the Apr 01 benefit change

Drug	"Turned off"	"Turned back on"
Antifungals for onychomycosis [itraconazole (Sporanox), terbinafine (Lamisil)]	10 April 01	1 May 01
Antifungals for onychomycosis [(ciclopirox top solution (Penlac)]	NA	10 May 01
COX-2 inhibitors [celecoxib (Celebrex), rofecoxib (Vioxx)]	14 April 01	30 April 01
Etanercept (Enbrel)	14 April 01	30 April 01
Sildenafil (Viagra)	10 April 01	10 May 01

B. *Cost avoidance from NMOP prior authorizations (PAs)* – Shana Trice (PEC) reported that cost avoidance analyses were not completed for this quarter due to the temporary suspension of the NMOP PA Program. Merck-Medco is now supplying data that identifies new and refill prescriptions, which should improve the accuracy of cost avoidance analyses.

C. *Utilization of the NMOP and retail network pharmacies for drugs subject to PA* – An analysis of the potential shift of patients with prescriptions for COX-2 inhibitors from the NMOP to the retail network is underway, using data from PDTS.

D. *Revision of NMOP PA forms* – Changes to clinical rationale language for the COX-2 inhibitors were delayed by the temporary suspension of the NMOP PA program. Further discussion with Merck-Medco is required to incorporate clinical rationale language for this drug class into the fax forms used by Merck-Medco. Changes to clinical rationale language for the antifungals for onychomycosis to reflect safety announcements by the Food and Drug Administration (FDA) concerning terbinafine and itraconazole are in progress.

E. *Status of the PA for sildenafil (Viagra) in the NMOP and retail network* – MAJ Bellemin commented that the sildenafil PA is responsible for the most patient complaints of all PAs in the NMOP. He suggested that quantity limits already in effect (6 tabs per 30 days for the retail network; 18 tabs per 90 days for the NMOP) might be sufficient to control over-utilization without a PA. The PA for sildenafil was established by a Health Affairs policy, so the PA cannot be discontinued unless the policy is changed. Other drugs similar to sildenafil may be on the market soon, which may provide an impetus to change the sildenafil policy. .

COL Davies commented that the information in the current sildenafil PA regarding drug interactions and contraindications has a questionable impact on prescribing, since the second most frequently reported potential drug-drug interaction in PDTS is concomitant sildenafil and nitrate use. The committee agreed that the potential impact of removing the PA for sildenafil should be assessed more completely before recommending any policy changes to Health Affairs. Bill Hudson (Humana) will present data from the MCSCs and MAJ Bellemin will present data from the NMOP at the next meeting for assessment of the potential impact of removing the sildenafil PA.

8. **RATIONALE FOR QUANTITY LIMITS** – COL Remund reported that the PEC will add to its website an explanation of the rationale for placing quantity limits on certain drugs.

9. **PROPOSED QUANTITY LIMITS FOR OXYCONTIN** – Bill Hudson (Humana) proposed a 120 tablet per 30 days quantity limit for oxycodone extended release (Oxycontin) for the NMOP and retail network due to increasing abuse and misuse of this product.

Some committee members stated that the quantity limit would adversely affect patients who have a legitimate need for large quantities of Oxycontin, and may have little or no impact on patients who are abusing or diverting it. Person who are abusing or diverting Oxycontin will more likely submit prescriptions to multiple pharmacies than a single prescription for a large quantity. Pharmacists can use the information in patient profiles and the advisory messages provided by PDTS to identify these patients. A quantity limit on Oxycontin may set a precedent for limits on other pain medications, which would be inconsistent with the movement toward more adequate treatment of pain. The committee voted against the proposed quantity limit.

10. **REVIEW OF INJECTABLE MEDICATIONS AVAILABLE THROUGH THE NMOP** – The PEC review of the NMOP Covered Injectables list identified goserelin (Zoladex) and leuprolide (Lupron) depot as items that are not labeled for self-administration or commonly used in an outpatient setting. During the 4-month period from Mar – Jun 2001, 15 patients received prescriptions for Zoladex and 63 patients received prescriptions for Lupron Depot from the NMOP.

Lupron is available in both subcutaneous and depot dosage forms and is indicated for a variety of disease states. The subcutaneous form is commonly administered in the home setting. Lupron Depot is an intramuscular injection and is not designed for self-administration, but several facilities have programs that teach caregivers to give IM dosage forms such as Lupron Depot at home (e.g., monthly injections for precocious puberty). The committee decided that both the subcutaneous and depot formulations of Lupron should remain on the NMOP Covered Injectables List.

Goserelin (Zoladex) is an implant that requires insertion under sterile conditions and is not routinely administered outside of a hospital or clinic. The assumption is that virtually all Zoladex prescriptions are taken to physician offices or clinics for administration. The committee's understanding is that TRICARE regulations and policies do not specifically prohibit patients from getting prescriptions filled at the NMOP or retail pharmacies for subsequent administration in a physician office or clinic. The committee decided that Zoladex should remain on the NMOP Covered Injectables List.

The committee then discussed numerous issues pertaining to patients obtaining injectable products from the NMOP or retail pharmacies for subsequent administration in provider offices or clinics:

- Safety concerns about patients transporting hazardous products such as cytotoxic agents
- Quality control concerns about products that are sensitive to heat or moisture
- Payment of unnecessary copays by patients if the injectable product should have been provided as part of the physician office visit
- Payment of excess costs by the government if the expense of the injectable product should have been covered as part of the payment for the office visit
- Coverage for drugs administered in provider offices under Medicare Part B for some patients
- The fact that some providers might not stock certain injectables in their offices, making it necessary for the patient to obtain these products from the NMOP or a retail pharmacy
- The need to allow for medical necessity overrides of any general policy concerning injectable medications. For example, some injectable drugs have clinically accepted uses via non-injectable routes of administration (e.g., colistin vials used for home nebulization).

COL Davies requested that the DoD P&T Committee provide a recommendation to TMA concerning any needed policy interpretations or policy changes. A subcommittee was appointed to work on this issue. Subcommittee members are: LtCol (select) George Jones (chair), LTC (P) Joel Schmidt, MAJ Brett Kelly, MAJ Mickey Bellemin, and Bill Hudson. LTC DeGroff will provide data from the Pharmacy Data Transaction Service to the workgroup. COL Remund noted that the data needs go beyond what PDTS could provide, since the workgroup also needed to know what drugs patients were having difficulty getting. MAJ Bellemin said that the NMOP had a list of complaints, while COL Davies can supply information from congressional complaints to TMA and some of the MCSCs have records of prescription denials.

11. CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN) – Because of specialized educational requirements mandated by the FDA, dofetilide is only available for outpatient use through Stadtlander's Pharmacy/CVS Procare (which is a non-network pharmacy for DoD beneficiaries). LTC DeGroff reported that a centralized policy and procedure is being worked out with Pfizer so that DoD patients are not forced to pay the copay for a non-network pharmacy. Under the procedure, all prescriptions outside the MTF would still go through Stadtlander's/CVS Procare, but would be paid through a central billing mechanism. The patient would pay only the copay, with the rest billed to a central account at FSS pricing, and the drug would be mailed from Stadtlander's/CVS Procare to the patient. COL De Groff estimated that about 220 patients in DoD might use this process. Clinical reviews for dofetilide, which has multiple drug-drug interactions, are being done out of the PDTS database.

12. ADJOURNMENT – The meeting adjourned at 1200 hours. The next meeting will be held at 0800 on 15 November 2001 in the Washington DC area (specific location to be determined). All agenda items should be submitted to the co-chairs no later than 19 October 2001.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Almotriptan 6.25- and 12.5-mg tablets (Axert; Pharmacia & Upjohn)	7 May 01; treatment of migraine with and without aura in adults. Not intended for the prophylactic therapy of migraine or in the treatment of basilar or hemiplegic migraine. Safety and effectiveness in cluster headaches not established.	Added to NMOP Formulary	**Quantity Limits** **6.25-mg tab:** NMOP: 36 tablets per 90 days; Retail Network: 12 tablets per 30 days **12.5-mg tabs:** NMOP: 36 tablets per 90 days; Retail Network: 12 tablets per 30 days **Rationale for Quantity Limits** Safety and efficacy of treating more than 4 migraines a month with this class of drugs not established. Patients experiencing more frequent migraines are likely to be candidates for routine prophylactic treatment (e.g., with beta-blockers or selective serotonin reuptake inhibitors). Recommended quantity limits for the retail network are based on the treatment of 4 headaches a month, rounding up to the next full box, if necessary. Quantity limits for the NMOP were calculated as three times the limit for the retail network to maintain consistency across points of service. **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** sumatriptan oral and sumatriptan autoinjector
Drospirenone 0.3 mg / ethinyl estradiol 30 mcg tablets (Yasmin; Berlex)	11 May 01; prevention of pregnancy	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class**: multiple oral contraceptives
Desogestrel/ ethinyl estradiol tablets (Cyclessa; Organon)	22 Dec 2000; prevention of pregnancy	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** multiple oral contraceptives
Valganciclovir tablets (Valcyte; Syntex)	29 March 2001; treatment of cytomegalovirus retinitis in AIDS patients	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** None

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Albuterol sulfate 3 mg and ipratropium bromide 0.5 mg per 3 mL (DuoNeb Solution for Inhalation; Dey Labs)	21 Mar 2001; bronchospasm associated with COPD in patients requiring more than one bronchodilator medication	Added to NMOP Formulary	**Quantity Limits** NMOP: 540 vials per 90 days; retail network: 180 vials per 30 days **Rationale for Quantity Limits** Based on maximum recommended doses (up to 6 treatments per day). Quantity limits for both ipratropium and albuterol vials for inhalation are currently in effect. **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** albuterol and ipratropium vials for inhalation
Insulin aspart injection (NovoLog; Novo Nordisk)	8 Jun 2000 (available Sep 2001); with an intermediate or long-acting insulin for treatment of adult patients with diabetes mellitus or those with hyperglycemia	Added to the NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** No rapid-acting insulin analogs on the BCF; insulins on the BCF are Novolin N, R, 70/30

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES** (See Minutes of the 15 August DoD P&T Executive Council Meeting)
   A. *Additions to the BCF*
      1) Rabeprazole oral – effective 1 Oct 2001
      2) Montelukast oral
      3) Amiodarone oral
      4) Clindamycin phosphate 1% topical solution
   B. *Deletions from the BCF*
      1) Cerivastatin oral – due to market withdrawal
      2) Omeprazole oral – effective 1 Oct 2001
      3) Quinidine sulfate oral
      4) Quinidine gluconate oral
      5) Primidone oral
   C. *Changes and clarifications to the BCF*
      1) The PPI class will be open effective 1 Oct 2001. As of 1 Oct 2001, MTFs must add rabeprazole (Aciphex) to their formularies (see above), but may have other PPIs on their formularies in addition to rabeprazole.
2. **NMOP FORMULARY CHANGES**
   A. *Additions to the NMOP Formulary* (See Appendix A for details)
      1) Almotriptan tablets (Axert; Pharmacia & Upjohn) - quantity limits apply
      2) Drospirenone 0.3 mg and ethinyl estradiol 30 mcg tablets (Yasmin; Berlex)
      3) Desogestrel 0.1/0.125/0.15 mg and ethinyl estradiol 25 mcg tablets (Cyclessa; Organon)
      4) Valganciclovir tablets (Valcyte; Syntex)
      5) Albuterol sulfate 3 mg and ipratropium bromide 0.5 mg per 3 mL (DuoNeb Solution for Inhalation; Dey Labs) – quantity limits apply
      6) Insulin aspart injection (NovoLog; Novo Nordisk)
   B. *Exclusions from the NMOP Formulary* – None
3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**
   A. Quantity limit for almotriptan 6.25- and 12.5-mg tablets (Axert; Pharmacia & Upjohn) – NMOP: 36 tablets per 90 days; retail network: 12 tablets per 30 days
   B. Quantity limit for albuterol sulfate 3 mg and ipratropium bromide 0.5 mg per 3 mL (DuoNeb Solution for Inhalation; Dey Labs) – NMOP: 540 vials per 90 days; retail network: 180 vials per 30 days
4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)** – None

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **15 August 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 15 August 2001 at the Non-Commissioned Officers Club, Ft. Sam Houston, TX. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
CAPT Robert Rist	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board representative

MEMBERS ABSENT

COL Rosa Stith, MC	Army
Dick Rooney	Department of Veterans Affairs

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TRICARE Management Activity
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Gary Blamire, MSC	Lead Agent Office, Region 6
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
SFC Tom Bolinger	DoD Pharmacoeconomic Center
SFC Augustin Serrano	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Carol Scott	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES –The minutes from the last meeting were accepted as written.

4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

TMA recently released AMP funds for FY 2001 to the military services. Based on prime vendor data, MTFs spent $37.3 million on AMP drugs during the first nine months of FY 2001 (see Appendix A). Total AMP expenditures for FY 2001 will likely be close to the projected figure of $50 million.

5. PROGRAM BUDGET DECISION 812

Program Budget Decision (PBD) 812, approved by the Deputy Secretary of Defense on 21 June 2001, increases MTF pharmacy funding by $307.1 million in FY 2002 to recognize the cost growth experienced in FY 2001. PBD 812 also funds MTF pharmacies at a 15% annual growth rate through FY 2007. MTF pharmacy expenditures will be reviewed annually to determine the adequacy of the revised program funding, and it will be adjusted accordingly. The PBD recognizes the fact that inadequate funding of MTF pharmacies can cause beneficiaries to fill their prescriptions in the private sector at much higher cost to the government.

6. COX-2 INHIBITORS

At the last meeting, the Council agreed that management of the COX-2 inhibitors should ideally focus on two issues: accurately and efficiently targeting COX-2 therapy to those patients at greatest risk for gastrointestinal (GI) adverse events, and reducing the unit cost of COX-2 inhibitors.

A. *Formulary status of COX-2 inhibitors and the use of targeting programs at MTFs*

A PEC survey of MTFs in August 2001 found that 54% of the MTFs have no COX-2 inhibitors on formulary and 77% of the MTFs have a program to target COX-2 inhibitor therapy (see Table 1). Most MTFs use the NMOP prior authorization criteria to target therapy.

Table 1: Formulary Status and Targeting Programs for COX-2 Inhibitors at MTFs

Service	MTFs responding	COX-2s on formulary			MTFs with Targeting Program
		None	One*	Both	
Navy	**14**	12	0	2	8
Air Force	**19**	6	7	6	19
Army	**25**	13	4	8	18
Total	**58**	**31 (53%)**	**11 (19%)**	**16 (28%)**	**45 (78%)**

* 10 MTFs had celecoxib and 1 MTF had rofecoxib

B. *Use of COX-2 inhibitors in the Military Health System (MHS)*

Table 2 displays the number of prescriptions filled for COX-2 inhibitors and traditional NSAIDs at the various MHS outpatient pharmacy points of service during July 2001.

Table 2: Prescription fills for COX-2 Inhibitors and Traditional NSAIDs in the MHS, July 2001

	MTF prescriptions	MCSC retail network prescriptions	NMOP prescriptions	Total
COX-2 inhibitors	45,345 (13%)	40,094 (37%)	12,826 (43%)	98,265 (20%)
Traditional NSAIDs	298,799 (87%)	67,960 (63%)	17,306 (57%)	384,065 (80%)
Total	344,144	108,054	30,132	482,330

Source: Pharmacy Data Transaction Service Customer Service Support Center

C. *Therapeutic interchangeability of COX-2 inhibitors*

A significant reduction in unit cost would likely be achieved by a closed class contract that selects a single COX-2 inhibitor for the BCF, but a closed class contract is feasible only if the drugs are therapeutically interchangeable. Additional safety data concerning rofecoxib and celecoxib recently became available due to the release of FDA advisory committee briefing documents and reviews of additional data from two large trials—the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-term Arthritis Safety Study (CLASS). These data were submitted to the FDA Arthritis Advisory Committee to support manufacturers' requests to remove NSAID-class GI warnings from product labeling. (The review documents represent the opinions of reviewers and not final conclusions of the FDA, which has not yet made a final determination.) The Council assessed various concerns about the therapeutic interchangeability of celecoxib and rofecoxib, including two key issues that arose from review of this additional information.

1. *Vioxx Gastrointestinal Outcomes Research study (VIGOR)* – Data from the VIGOR trial showed an increased risk of serious thrombotic cardiovascular events for rofecoxib compared to naproxen. The rate of confirmed thrombotic cardiovascular serious adverse events was 1.67 per 100 patient-years for the rofecoxib group and 0.70 per 100 patient-years for the naproxen group (RR 2.37; 95% CI 1.39 – 4.06; p=0.0016). The difference in the composite measure was primarily due to a difference in the incidence of myocardial infarctions between the rofecoxib and the naproxen group. These results could be explained by either a prothrombotic effect of rofecoxib or an antithrombotic cardioprotective effect of naproxen. See Appendix B for a more detailed discussion of VIGOR results.
2. *Celecoxib Long-term Arthritis Safety Study (CLASS)* – Published results of the CLASS trial were limited to data obtained during the first six months of study participation, although about 35% of patients completed nine months or more of treatment. Published results did not show a significant difference in the primary endpoint of the study [annualized incidence of confirmed complicated UGI events (perforations, obstructions, and GI bleeds)] between celecoxib and the pooled group of comparator non-steroidal anti-inflammatory drugs (NSAIDs) in the overall study population. There was a significant difference in the primary endpoint in the subgroup of patients not taking low dose aspirin.

   Results from the entire study period did not show a significant difference for the primary endpoint in either the overall study population or in the subgroup of patients not taking aspirin. The differences between the six-month and entire study period data appeared to be due to the occurrence of relatively more confirmed complicated UGI events in the celecoxib group than in the NSAID group in the time period subsequent to the first six months of study participation.

   These results raise doubts about the GI protective effects of celecoxib. The additional data also suggest that the statistically significant differences in GI safety endpoints between celecoxib and the pooled NSAID group are primarily due to differences between celecoxib and ibuprofen; celecoxib was not statistically significant from diclofenac for any patient group or endpoint. This finding raises additional doubts about the generalizability of CLASS results to patients receiving "traditional" NSAIDs not tested in the CLASS trial. See Appendix B for a more detailed discussion of CLASS results.
3. *Lack of rheumatoid arthritis indication for rofecoxib* – Rofecoxib is not currently indicated for rheumatoid arthritis (RA). Merck filed an application for a supplemental NDA for an indication for RA in March 2001 and has submitted additional studies to the FDA.
4. *Edema and hypertension* – Like traditional NSAIDs, both celecoxib and rofecoxib have been shown to increase blood pressure and produce edema. It is not clear whether there is a clinically significant difference in the propensity of the two drugs to produce such effects. Studies suggest a small, dose-related increase in edema and hypertension with rofecoxib, especially at 50 mg QD. A dose-response relationship has not been clearly shown for celecoxib.

5. *MTF survey regarding therapeutic interchangeability* - A survey was sent to lead agent pharmacists to ascertain the opinions of MTFs in their regions. The survey focused on the consensus opinions of facility P&T committees, not individual provider opinions. Lead agent pharmacists had the option of reporting individual MTF responses or submitting a single consensus response from their entire region. The survey included a clinical review comparing celecoxib and rofecoxib and a fact sheet outlining possible scenarios for contracting and/or BCF status. Questions about possible contracting and/or BCF status were to be answered under the assumption that the Program Budget Decision 812 would provide MTFs with adequate funding for these agents. Responses to the survey are summarized in Table 3.

Table 3: Responses to the COX-2 Interchangeability Survey

Region			1	2	3	4	5	6	7/8	9	10	11	12	Summary
Number of facilities responding			12	5	4	0	*	6	*	2	4	2	11	
% of patients whose initial clinical needs are met by	Celebrex	>90%	5	2	2			4		0	1	1	5	20
		75-90%	3	1	0			1		0	3	0	4	12
		<75%	3	2	2		X	1	X	2	0	1	2	14
	Vioxx	>90%	6	2	2			3		0	2	1	6	18
		75-90%	1	2	0			1	X	1	2	0	3	10
		<75%	4	1	2		X	2		1	0	1	2	12
Product more likely to fail		Equal	10	4	4		X	1		1	2	1	10	34
		Celebrex	1					1	X		1		1	5
		Vioxx								1	1			2
Relative acceptability of management options – means of individual responses (1 = Most acceptable; 5 = Least acceptable)														
Closed class contract			3.5	4	2.5		2	1	3		5	3	1.5	2.8
Add specific agent in open class			2	2	2.5		3	3	2	1.5	2	2	1.5	2.2
Add requirement for agent but do not specify			1	1	4		5	2	1	1.5	1	4	3.5	2.4
Add both agents to BCF			3.5	3	5		4	5	4		3	5	5	4.1
Add neither agent to BCF			5	5	1		1	4	5		4	1	3.5	3.3

* Consensus response from entire region only

D. *VA/DoD Clinical Review*

The PEC and the VA PBM are collaborating on a clinical review of the COX-2 inhibitors, but the review is not complete yet.

E. *P&T Executive Council Conclusions*

Based on the available safety and efficacy data and the lack of a RA indication for rofecoxib, the Council could not conclude that celecoxib and rofecoxib are therapeutically interchangeable. MTFs vary significantly in their support for a closed class contract. The Council does not support a closed class contract for a COX-2 inhibitor at this time.

The analysis of all the data for the CLASS study raises questions about the GI protective effects of celecoxib. The VIGOR study raises concerns about a potential increase in risk of cardiovascular events with rofecoxib. The COX-2 inhibitors are no more effective than traditional NSAIDs for treating osteoarthritis or rheumatoid arthritis. The COX-2 inhibitors cost much more than traditional NSAIDs. The Council concluded that a COX-2 inhibitor should not be added to the BCF at this time.

7. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

A. *Contract awards, renewals, and terminations*

- As of 1 August 2001, 47 joint VA/DoD national contracts have been awarded. Information on national pharmaceutical contracts, including NDC numbers and prices, is available on the DSCP website (www.dmmonline.com).
- Since the last meeting, DoD/VA single source contracts were awarded for the following drugs:
  - Carbidopa/levodopa 25 mg/100 mg and 50 mg/200 mg sustained action tablets, to Dupont Pharma
  - Glyburide 1.25mg, 2.5mg and 5mg tablets, to Pharmacia Corporation
  - Ointment Base (Absorbase 50% water-in-oil emulsion) 454- and 120-gram jars, to Carolina Medical Products
- The 21-count, 6-cycle package of ethinyl estradiol/ norethindrone tabs (Norinyl) was removed from the national contract effective 24 July 2001. The item may be purchased off the FSS at the same price. The 28-count packages remain on the contract.
- The albuterol inhaler contract will not be renewed due to continuing availability problems with all the chlorofluorocarbon (CFC) albuterol products.

B. *Financial impact of contracts* – Cost avoidance has been estimated by subtracting the actual expenditures for the "market basket" of products affected by a contract from the expenditures that would have occurred if the contract did not exist (based on the prices that existed before the contract took effect). This method is reasonably accurate for the first year of a contract, but changes in the "market basket" of products (e.g., new indications, generic availability, price changes for non-contracted drugs, introduction of new products, product withdrawals, etc.) make it difficult to accurately estimate "what would have been paid" if the contract did not exist in subsequent years. The Council agreed that the cost per patient-day of therapy or cost per member per month within therapeutic categories would be useful indicators of the financial impact of national pharmaceutical contracts and would avoid the ambiguities of cost avoidance estimates.

C. *Statin Contract* - The withdrawal of cerivastatin (Baycol) from the market leaves simvastatin (Zocor) as the only statin on the Basic Core Formulary (BCF) and the National Mail Order Pharmacy (NMOP) formulary. The P&T Executive Council concluded that simvastatin could meet the clinical needs of the vast majority of patients who previously took cerivastatin, so there is no need to add a second statin to the BCF or NMOP formulary at this time. Patients who previously took cerivastatin should be switched to simvastatin. Other statins should be used only when simvastatin will not meet the clinical needs of an individual patient.

The simvastatin contract requires the statin class to remain "closed" on the BCF and NMOP formulary. The simvastatin contract is in effect until February 2002, and there is an option to renew the contract to February 2003. The DoD P&T Executive Council will evaluate clinical and economic information regarding the statin class and make a

recommendation to the Defense Supply Center Philadelphia (DSCP) regarding the potential renewal of the simvastatin contract. The Council will consider the impact of new NCEP guidelines on statin usage; the potential availability of rosuvastatin (Crestor); and impending patent expirations (lovastatin - expected Dec 2001; pravastatin - expected early 2003).

The P&T Executive Council was informed that Merck would reduce the DoD contract prices for four of the five strengths of simvastatin effective 1 Sep 2001 (see Table 4).

Table 4: DoD Contract Prices for Simvastatin

Strength	Old Price	New Price (effective 1 Sep 01)
5 mg	$0.41	$0.38
10 mg	$0.62	$0.50
20 mg	$0.65	$0.60
40 mg	$0.94	$0.85
80 mg	$0.98	$0.98

D. *Proton pump inhibitor contract*

The contract for omeprazole (Prilosec) will expire on 30 September 2001 and will not be renewed because the omeprazole contract price would be much higher than the prices for other proton pump inhibitors. As a consequence, the proton pump inhibitor class will revert to an "open class" on the BCF as of 1 October 2001. The Council reviewed the safety, tolerability, efficacy, price/cost, and other factors associated with proton pump inhibitors.

Safety/Tolerability – The PPIs appear to have similar safety profiles. Early concerns about gastric enterochromaffin-cell hyperplasia and gastric cancer caused by chronic hypergastrinemia have not materialized in clinical practice.

Omeprazole may be the most likely to cause cytochrome P450 drug interactions as it interacts preferentially with CYP2C19, inhibiting the metabolism of diazepam, phenytoin, and warfarin. Rabeprazole, pantoprazole and lansoprazole do not appear to cause clinically significant P450 drug interactions. Experience with esomeprazole is limited. Omeprazole is Pregnancy Category C; the other 4 PPIs are Category B.

Efficacy – When used at appropriate doses, all the PPIs are efficacious for the treatment of a variety of acid-related disorders, including gastroesophageal reflux disease (GERD) and erosive esophagitis. More than 20 published, double-blind, randomized, head-to-head trials used omeprazole as the comparator drug. These studies showed that, in most patients, omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, and rabeprazole 20 mg/day relieve GERD symptoms within several days and heal esophageal erosions within 4 - 8 weeks of initiating therapy. Reported differences in the duration of antisecretory effect vary between patients and do not necessarily translate into improved clinical efficacy. Lansoprazole 30 mg/day and rabeprazole 20 mg/day may provide more rapid relief of GERD symptoms when compared with omeprazole 20

mg./day, but the differences are usually observed only in the first few days of treatment. Esomeprazole may have a faster onset of healing of esophageal erosions, but healing rates at 12 weeks are similar to those reported with omeprazole.

Price/Cost

Table 5: DoD Prices for Proton Pump Inhibitors

Generic	Brand	Dose	Current Price	After 1 Oct
Rabeprazole	Aciphex	20 mg	$0.22 (FSS)	$0.22 (FSS)
Lansoprazole	Prevacid	30 mg	$2.06 (FSS)	$2.06 (FSS)
Pantoprazole	Protonix	40 mg	$1.27 (FSS)	$1.27 (FSS)
Omeprazole	Prilosec	20 mg	$1.09 (contract)	$2.02 (FSS)
Esomeprazole	Nexium	20 mg	$2.35 (FSS)	$2.35 (FSS)
FSS = Federal Supply Schedule; BPA = Blanket Purchase Agreement				

Other Factors

- *Availability of generic omeprazole* – AstraZeneca has received pediatric exclusivity for Prilosec through 5 Oct 2001. The FDA has granted tentative approval for generic versions of Prilosec to two generic companies: Andrx for 10-, 20- and 40-mg delayed release capsules and GenPharm for 10- and 20-mg delayed release capsules. Due to an agreement between the two companies, Andrx would be considered the "first-to-file" and thus should be the only generic available for the most commonly used 20-mg strength of omeprazole for up to 180 days following approval. It is unknown when generic omeprazole will be available, as lawsuits involving at least 4 generic companies are underway or pending.
- *VA usage* - The VA is currently converting the majority of their patients from lansoprazole, which was previously their contract agent, to rabeprazole. Lansoprazole continues to be available to VA facilities at a BPA price of $0.55 per capsule.
- *Direct-to-consumer (DTC) advertising* - AstraZeneca is currently running an intensive DTC advertising campaign attempting to convince patients to switch from omeprazole to esomeprazole.
- *Provider survey results* – A survey was sent to GI specialists and primary care providers in all three services, who were also asked to forward the survey to other clinicians. The VA PPI class review and a supplemental fact sheet from the PEC were sent along with survey questions. A total of 28 responses were received from 15 Army, 11 Air Force, and 2 Navy providers. The majority of responses were from family medicine (10), followed by GI specialists (6); general surgery (3); internal medicine, primary care, flight medicine, unknown specialty (2 each); and pulmonary/critical care (1). Summary results are shown in Table 6 following.

  Comments from providers generally supported the therapeutic interchangeability of PPIs. Most agreed that using the least costly PPI would be appropriate to treat the majority of patients.

Several providers mentioned the need for alternate PPIs for patients with swallowing difficulties. Only lansoprazole has an oral suspension. Labeling for lansoprazole, omeprazole, and esomeprazole capsules indicates they can be opened and sprinkled on applesauce; rabeprazole and pantoprazole have no alternative dosage forms, but are relatively small tablets. Providers also mentioned the desire to have an intravenous PPI available. Only pantoprazole is available in an intravenous formulation.

Two providers commented negatively on the DTC campaign for esomeprazole. Two Air Force providers mentioned the fact that omeprazole is the only PPI specifically approved for Air Force aircrew waiver.

Table 6: PPI Provider Survey

	Strongly Agree	Agree	Neither Agree or Disagree	Disagree	Strongly Disagree
All the PPIs currently available are likely to be effective for treating the conditions for which I typically prescribe PPIs.	14	13	0	1	0
The differences in FDA-approved indications between these products have little clinical relevance when treating most patients.	8	17	0	3	0
The faster time to relief of symptoms reported by AstraZeneca for esomeprazole has little to no clinical significance.	5	16	4	2	0
The faster time to relief of symptoms reported for rabeprazole has little to no clinical significance.	4	16	5	2	0
Price should be a consideration when providers decide which of these agents to prescribe.	13	14	1	0	0
I have sufficient concerns regarding the safety, efficacy, or patient acceptability of the other available PPIs that I will continue to prescribe Prilosec after October 1st regardless of price.	0	2	0	13	12

After considering safety, tolerability, efficacy, price, and patient acceptability, which of the following PPIs, if available on formulary after October 1, would I feel comfortable using.

Drug	Definitely Use	Consider Use	Use with reservations	Never Use
Omeprazole	14	7	3	1
Rabeprazole	18	8	1	0
Lansoprazole	13	13	0	0
Pantoprazole	7	16	2	1
Esomeprazole	8	8	5	3

The Council concluded that there are no clinical or economic reasons to pursue another closed class contract in this drug class. The Council voted to remove Prilosec from the BCF and add rabeprazole (Aciphex) to the BCF. These BCF changes take effect on 1 Oct 2001. MTFs may have other PPIs on their formularies in addition to rabeprazole as of 1 Oct 2001.

E. *Status of contracting initiative for nasal corticosteroid inhalers* – The DoD P&T Executive Council concluded at the November 2000 meeting that a closed class contract could be sought for a high-potency aqueous nasal corticosteroid. The Council identified five products that could compete for the contract: budesonide 32 mcg/spray, fluticasone 50 mcg/spray, triamcinolone 55 mcg/spray, mometasone 50 mcg/spray, and beclomethasone 84 mcg/spray. The VA recently completed its class review of nasal corticosteroid inhalers. The VA wants to include flunisolide (Nasarel) in the solicitation for a closed class contract. The Council asked the PEC to update its analysis of the nasal steroid class and recommend to the Council whether or not flunisolide should be included in the solicitation.

F. *Status of potential contracting initiative for leukotriene antagonists* – The VA is currently evaluating montelukast (Singulair) and zafirlukast (Accolate) for potential contracting. The 5-lipoxygenase inhibitor Zileuton (Zyflo) is not being considered due to several clinical disadvantages, including four times daily dosing and an increased risk of drug interactions and hepatotoxicity compared to the other two agents. This drug class has been proposed as a potential joint DoD/VA contracting initiative. The BCF currently states that each MTF must have a leukotriene antagonist on formulary, but the selection of the specific product is left to the MTF.

Safety/Tolerability – Placebo-controlled trials with both agents have shown a low incidence of adverse effects. GI symptoms and headache are reported most commonly. In trials comparing leukotriene antagonists with inhaled corticosteroids, both montelukast and zafirlukast were associated with higher discontinuation rates due to adverse events than inhaled corticosteroids.

Both products have been associated with elevations in liver function tests, although confounding factors make causality difficult to assess. One serious adverse reaction, Churg Strauss syndrome, has occurred during steroid tapers with both montelukast and zafirlukast, but may have been associated with "unmasking" of a pre-existing condition. Zafirlukast has clinically significant drug interactions with theophylline and warfarin. Clinically significant drug interactions have not been reported for montelukast.

Efficacy

Adult patients

- *Comparative trials with inhaled ß-agonists*: Studies have shown that adding a leukotriene antagonist to a short acting ß-agonist reduces the occurrence of asthma symptoms and the use of ß-agonists more than placebo.
- *Comparative trials vs. inhaled corticosteroids*: Although similar asthma exacerbation rates have been reported, inhaled corticosteroids significantly improve quality of life, lung function, and symptom control compared with the leukotriene antagonists.
- *Asthma monotherapy trials*: There are no published head-to-head trials with zafirlukast and montelukast. When two individual studies with similar trial design are compared, montelukast was slightly superior to zafirlukast in terms of FEV1 (forced expiratory volume in one second), PEFR (peak expiratory flow rate), and

prn albuterol use at 12 weeks. However, low-dose fluticasone was superior to either leukotriene inhibitor.

- *Combination of leukotriene antagonists with inhaled corticosteroids*: There are no head to head comparisons, and the trial designs of the available studies are too dissimilar to make comparisons

Pediatric patients

- Head to head comparisons between montelukast and zafirlukast are not available. The trial that was the basis for montelukast's pediatric labeling is only available in the package insert and has not been published in a peer-reviewed journal. A pediatric study comparing zafirlukast with low-dose fluticasone has been published. Both montelukast and zafirlukast improve symptoms and lung function compared with placebo. Inhaled steroids show similar exacerbation rates compared to leukotriene antagonists, but result in better improvements in lung function and symptoms.

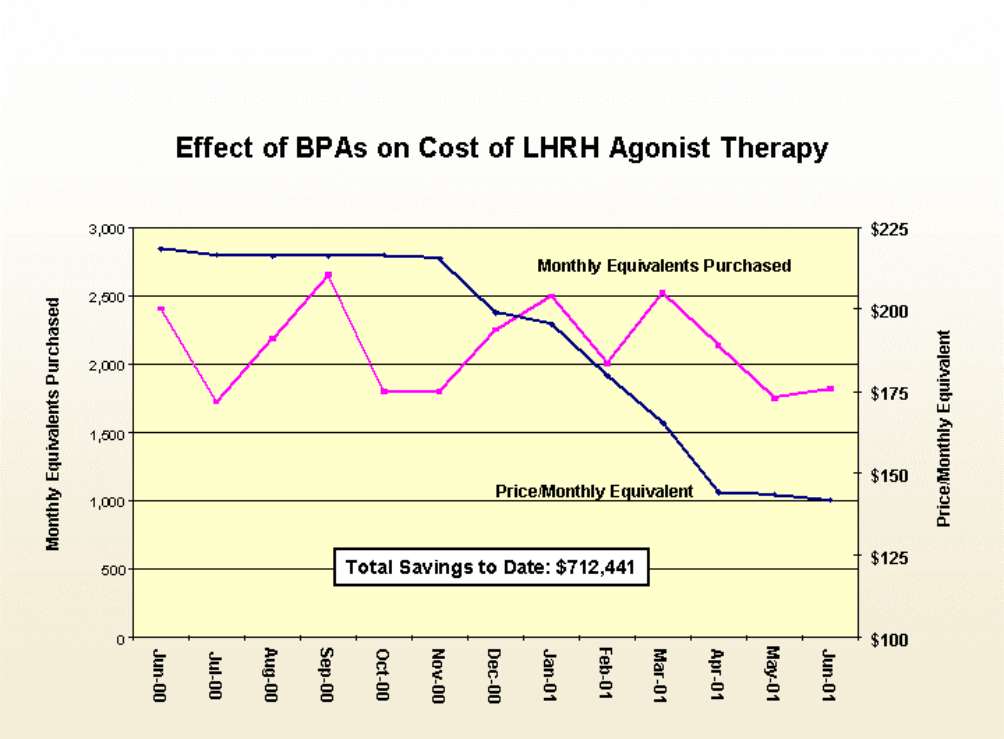
Other Factors

- Based on total tablets purchased, market shares for montelukast and zafirlukast in DoD MTFs are approximately 93% and 7%, respectively. Purchases by VA facilities are more evenly split between the two drugs—43% of leukotriene antagonist tablets purchased are montelukast; 56% are zafirlukast. Zafirlukast is typically dosed twice daily.
- Montelukast is dosed once daily and has FDA approval for patients as young as 2 years of age. A 4-mg chewable tablet formulation is available for children 2-5 years of age. Zafirlukast is dosed twice daily. It is FDA-approved for patients 7 years of age and older.

The Council concluded that montelukast and zafirlukast are not therapeutically interchangeable and that a closed class contract for a leukotriene inhibitor is not feasible for DoD. After considering the safety, tolerability, efficacy, and other factors associated with the leukotriene antagonists, the Council voted to add montelukast to the BCF.

G. *Non-sedating antihistamine contract* – Increases in prescription market share for fexofenadine (Allegra) and decreases in market share for loratadine (Claritin) indicate that MTFs are successfully implementing the non-sedating antihistamine contract. By the end of July 2001, the market share for fexofenadine (as a percent of all prescriptions for non-sedating antihistamines dispensed at MTF pharmacies) increased from 50% prior to the contract to nearly 80%. The prescription market shares for fexofenadine and loratadine remained stable in the retail pharmacy networks and the NMOP, indicating that MTFs are maximizing the use of fexofenadine without shifting loratadine prescriptions into the retail pharmacy network or NMOP. Since the contract took effect, the average cost per non-sedating antihistamine tablet/capsule purchased by MTFs has dropped by 33%, from $0.87 to $0.58. Appendix C contains market share and cost graphs for the non-sedating antihistamines.

H. *Status of BPAs and potential contracting action for Leutinizing Hormone Releasing Hormone (LHRH) agonists* – The AstraZeneca Federal Account Director has stated that the Blanket Purchase Agreement (BPA) for goserelin (Zoladex) will stay in effect even if the 80% market share requirement is not met by 1 Sep 2001. The Zoladex and leuprolide (Lupron) BPAs have reduced the weighted average cost per monthly equivalent of LHRH agonist therapy for prostate cancer by 35%, from $215 in November 2000 to $140 in June 2001. The BPAs yielded $712,000 in cost avoidance for MTFs from November 2000 to June 2001.



Lupron and Zoladex are generally considered equivalent in safety and efficacy for treatment of prostate cancer. The therapeutic interchangeability of these products hinges on tolerability and other factors that affect patient or provider acceptance of either product. CAPT Torkildson (PEC) obtained input from Urology specialty leaders and other providers:

- Several providers reported that patients had been switched from one product to the other without problems.
- Zoladex must be implanted rather than simply injected, so administration of Zoladex consumes more physician time. Some MTFs improve the efficiency of Zoladex administration by training non-physicians to administer the product.
- Lupron has a 4-month dosage form; Zoladex does not.
- Some providers expressed concern regarding lack of experience with one or the other products.
- There was general agreement that the potential for decreased cost is sufficient reason to seek a contract.

The dosage forms of Lupron and Zoladex that would compete for this contract are not used exclusively for prostate cancer. The PEC estimates that 10% of the Lupron usage and 2% of the Zoladex usage are for conditions other than prostate cancer. However, the age and sex specificity of prostate cancer allows contract compliance to be monitored relatively easily.

The Council voted to support a joint VA/DoD contract for an LHRH agonist for the treatment of prostate cancer.

8. THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS (CURE) TRIAL

The Council reviewed preliminary summary information from the CURE trial. (Complete results of the trial were subsequently published in the 16 Aug 2001 issue of the New England Journal of Medicine.) The CURE trial enrolled approximately 12,500 patients with unstable angina and non-ST elevation MI presenting within 24 hours of the onset of symptoms. Patients were randomized into two groups: aspirin alone (75 to 325 mg QD) or aspirin plus clopidogrel (300 mg immediately, then 75 mg QD). Follow-up was for an average of 9 months. A 20% reduction in the composite endpoint of cardiovascular death, nonfatal MI, or stroke was reported for the combination of clopidogrel plus aspirin compared to aspirin alone. The combination reportedly had both an early (within 2 hours) and sustained benefit relative to aspirin alone. A significant increase in major (but not life-threatening) bleeds was reported in patients receiving both aspirin and clopidogrel, but there was insufficient information to adequately assess the severity of the incremental risk of bleeding.

Clopidogrel is currently indicated for prevention of stroke and/or MI in patients with aspirin allergy and for short-term use following cardiac stent placement. Clopidogrel is not on the BCF. The Council agreed that it would be premature to consider clopidogrel for the BCF on the basis of preliminary data, but asked the PEC to review results of the published study and make recommendations.

9. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove quinidine from the BCF* – A pharmacist from an Army medical center requested removal of quinidine products from the BCF due to infrequent usage.

Meta-analyses have shown increased mortality rates in patients given quinidine during or after acute myocardial infarction and patients given quinidine after cardioversion for atrial fibrillation. Mortality rates in patients with ventricular arrhythmias were three times higher with quinidine than other Class I antiarrhythmics. In addition, the risk of torsade de pointes, a potentially fatal arrhythmia, is estimated to be 1.5% to 8% in patients treated with quinidine. (Some clinicians feel this may underestimate the true occurrence.) Current therapy recommendations relegate quinidine to second or third-line status for either atrial or ventricular arrhythmia. According to data from the Uniformed Services Prescription Database, MTF prescriptions for quinidine products have consistently decreased over the past 3 years to fewer than 200 prescriptions per month for quinidine sulfate and fewer than 1300 prescriptions per month for quinidine gluconate.

The Council voted to remove both quinidine sulfate and quinidine gluconate from the BCF. MTFs may choose to remove or retain these products on their formularies.

B. *Request to remove primidone from the BCF* – A pharmacist from an Army medical center requested removal of primidone from the BCF due to infrequent usage.

Primidone is FDA approved for treatment of partial complex seizures but is rarely used for that indication. Its primary use is off-label for the treatment of essential tremor. Safer, more tolerable alternatives are available for both seizure disorder and essential tremor. The DoD P&T Council voted to remove primidone from the BCF because it has no clinical benefit over agents already on the formulary. MTFs may choose to remove or retain primidone on their formularies.

C. *Request to add amiodarone to the BCF* – A primary care provider and a cardiologist from an Air Force teaching facility requested addition of amiodarone to the BCF based on current use of this drug in clinical practice.

Safety/Tolerability - Amiodarone carries a black box warning that lists potentially fatal toxicities, including proarrhythmic effects, pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis), and overt liver disease (in a few cases). Proarrhythmic effects appear to occur in less than 1% of patients, mostly in conjunction with electrolyte abnormalities or when used concurrently with other antiarrhythmics. This is a less frequent occurrence than seen in other antiarrhythmics. Pulmonary toxicity can be seen in 5% to 15% of patients, but has a good prognosis when the drug is discontinued.

The most common adverse effect of amiodarone is thyroid dysfunction; discontinuation of the drug is usually not necessary. Most other adverse effects are dose dependent. In general, smaller doses of amiodarone are required to treat atrial arrhythmias than ventricular arrhythmias. No other Class III antiarrhythmics are currently available.

Efficacy – Amiodarone is only FDA-indicated for the management of life-threatening recurrent ventricular fibrillation or hemodynamically unstable ventricular tachycardia, but use of the drug in clinical practice has changed significantly since its introduction in 1985. Amiodarone is now widely used to treat both atrial and ventricular arrhythmias. .

Other Factors – The VA developed a form to assist in monitoring amiodarone patients with regard to drug-drug interactions and timing of labs and other ancillary services (available at: www.vapbm.org/monitoring/amiodaron.htm). Guidelines intended for the use of primary care providers who follow patients on amiodarone have been issued by the North American Society of Pacing and Electrophysiology [Arch Intern Med 2000 (26 June); 160(12):1741-8]. Publication of guidelines for the treatment of atrial fibrillation by the American College of Cardiology and the American Heart Association are anticipated by the end of Aug 2001.

The Council added amiodarone to the BCF.

10. REVIEW OF ACNE MEDICATIONS FOR THE BCF

MAJ Barbara Roach reported on the PEC review of acne medications. The BCF currently lacks topical treatment choices for patients with acne who do not respond to over-the-counter benzoyl peroxide. The PEC evaluated the safety, tolerability, efficacy, cost, and historical MTF usage of topical acne medications and recommended the addition of clindamycin phosphate 1% solution and tretinoin cream 0.025% and 0.05% to the BCF. The PEC also recommended the removal of age restrictions for tretinoin cream in the NMOP and retail

pharmacies because it is commonly used for seborrheic keratoses (which occur in older adults).

The Council added clindamycin phosphate 1% solution to the BCF. Council members were concerned that the removal of age restrictions would allow tretinoin to be used for cosmetic treatment of photoaged skin (wrinkles and liver spots). The Council was uncertain as to whether the age restriction was specified in the Code of Federal Regulations, TRICARE policy, or the NMOP Statement of Work. Military service policies might also have age limits on tretinoin availability. The Council voted to table the decision on tretinoin until these issues are clarified.

11. OBTAINING INPUT FROM PROVIDERS

The PEC has substantially increased efforts to obtain input from physicians and pharmacists on formulary and contracting issues. A BCF request form is available for MTF personnel to recommend changes in the BCF. Teleconferences are conducted with the pharmacy consultants/specialty leaders and pharmacists representing each TRICARE region. The PEC has surveyed specialty consultants and MTF providers to obtain input on important drug classes such as COX-2 inhibitors, proton pump inhibitors, LHRH agonists, and low molecular weight heparins, but these are informal surveys instituted on a case-by-case basis. There is no formal, recognized, systematic method for MTF providers to routinely have input on formulary and contracting issues.

The Council appointed a subcommittee to explore ways to systematically obtain input from providers on formulary and contracting issues. Subcommittee member are COL Downs, LCDR Briski, and COL Davies or his designee.

12. The meeting adjourned at 1600 hours on 15 August 2001. The next meeting will be held in the Washington DC area (specific location to be determined) and is scheduled for 14 Nov 2001 at 0800. All agenda items should be submitted to the co-chairs no later than 19 October 2001.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

LIST OF APPENDICES

Appendix A: MTF Expenditures for Drugs Included in the Advances in Medical Practice (AMP) Program

MTF Expenditures On Amp Drugs, First Nine Months Of FY 01

Drug Name*	Air Force	Army	Navy	Grand Total
Abciximab	$254,828	$216,886	$75,396	$547,110
Alpha-1-Proteinase Inhibitor			$18,228	$18,228
Becaplermin	$62,291	$94,926	$43,818	$201,035
Cyclosporine	$322,159	$235,474	$178,033	$735,666
Cyclosporine Microemulsion	$662,783	$632,102	$628,818	$1,923,703
Dornase Alfa	$238,605	$136,393	$154,692	$529,690
Epoetin Alfa	$3,074,457	$3,640,225	$1,957,694	$8,672,375
Eptifibatide	$66,227	$299,967	$179,640	$545,834
Etanercept	$1,165,366	$825,910	$499,619	$2,490,896
Factor VIIa,Recomb		$4,218		$4,218
Filgrastim	$1,071,525	$1,379,019	$809,235	$3,259,779
Gemcitabine Hcl	$168,885	$296,224	$225,954	$691,062
Glatiramer Acetate	$368,394	$180,715	$100,230	$649,339
Infliximab	$251,723	$258,436	$332,440	$842,598
Interferon Beta-1a	$1,211,255	$979,842	$496,651	$2,687,748
Interferon Beta-1b	$374,021	$512,901	$332,929	$1,219,851
Interferon Gamma-1b,Recomb.	$41,678	$65,455	$35,905	$143,037
Irinotecan Hcl	$183,078	$427,646	$232,438	$843,162
Leflunomide	$152,077	$285,243	$171,167	$608,488
Mycophenolate Mofetil	$412,354	$518,043	$219,776	$1,150,173
Mycophenolate Mofetil HCl	$919	$2,082		$3,002
Palivizumab	$1,316,843	$1,401,470	$943,150	$3,661,463
Ribavirin/Interferon A-2b	$539,000	$1,168,805	$423,249	$2,131,054
Rituximab	$284,989	$956,443	$407,289	$1,648,721
Sargramostim	$17,853	$105,341	$8,348	$131,542
Sirolimus	$33,545	$75,817	$31,191	$140,554
Tacrolimus Anhydrous	$409,332	$367,998	$226,014	$1,003,344
Temozolomide	$122,356	$95,662	$67,134	$285,152
Tirofib Hc M-Hyd/Na Chlor 0.9%	$2,745	$21,087		$23,832
Tirofiban HCl M-Hydrate	$87,199	$55,477	$19,159	$161,835
Trastuzumab	$121,671	$269,967	$26,662	$418,300
Grand Total	$13,018,156	$15,509,775	$8,844,859	$37,372,790

* Celecoxib and rofecoxib were removed from the AMP list for FY 01

Appendix B: COX-2 Inhibitor Trials (VIGOR and CLASS)

1. Cardiovascular Safety Data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) Study

The 8076-patient VIGOR trial (NEJM 2000;343:1520-8) included patients with rheumatoid arthritis (RA) who were 50 years old (or 40 years old and receiving long-term glucocorticoids) and excluded patients on low-dose aspirin for cardiovascular prevention. Patients were randomized to rofecoxib 50 mg QD or naproxen 500 mg BID. The median follow-up was 9 months (range 0.5 – 13). Use of aspirin or non-study NSAIDs was not allowed.

A detailed analysis of VIGOR data concerning the occurrence of cardiovascular events is available from FDA briefing documents, available at *www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2.htm*. Overall, the rate of adjudicated thrombotic cardiovascular serious adverse events per 100 patient-years was 1.67 for rofecoxib vs. 0.70 for naproxen [relative risk (RR) 2.37; 95% confidence interval (CI) 1.39-4.06; p=0.0016]. The difference in the composite measure was primarily due to a difference in the incidence of myocardial infarctions between the rofecoxib and the naproxen group. For patients identified as potential candidates for low-dose aspirin, the difference in event rates was marked: 14.29 for rofecoxib vs. 2.94 for naproxen (RR 4.89; 95% CI 1.41-16.88; p=0.0122). For patients not considered candidates for low dose aspirin, the difference in events was less marked but still statistically significant: 1.16 for rofecoxib vs. 0.62 for naproxen (relative risk 1.88; 95% CI 1.03-3.45; p=0.041).

It has been suggested that naproxen, which is relatively COX-1 selective, may have antiplatelet effects similar to aspirin. This may explain the relatively lower incidence of thrombotic events with naproxen compared to rofecoxib, but, as stated by the FDA Advisory Committee review, a direct prothrombotic effect of rofecoxib cannot be ruled out. Whether the putative effect of naproxen in reducing cardiovascular thrombotic effects in the VIGOR trial is reasonable compared to expected results with aspirin is subject to debate. There are no trials assessing the ability of naproxen to reduce cardiovascular events.

Since RA patients appear to have a higher baseline risk for cardiovascular disease than patients with osteoarthritis (OA), the RA population in VIGOR may have been more sensitive to any potential thrombogenic effect of selective COX-2 inhibition than a population predominated by OA patients. In addition, the effect may be dose-related; the 50-mg daily dose used in VIGOR is at least two times higher than doses recommended for chronic use.

The proposed prothrombotic mechanism is related to cyclooxygenase inhibition. COX-1 mediates production of thromboxane A2, which promotes vasoconstriction, platelet activation and aggregation. COX-2 mediates production of prostaglandins at inflammatory sites as well as prostacyclin (PGI2), a vasodilator and inhibitor of platelet aggregation. If COX-2 is selectively inhibited, unopposed production of thromboxane could result in an increase in CV thrombotic effects. Compensatory mechanisms are known to exist. Whether this theoretical effect applies to celecoxib is unknown, but appears plausible based on the proposed mechanism.

2. Additional Results Concerning GI Protective Effects of Celecoxib from the Celecoxib Long-term Arthritis Safety Study (CLASS)

The Celecoxib Long-term Arthritis Safety Study (CLASS) was an 8059-patient trial that compared celecoxib (400 mg BID) to diclofenac (75 mg BID) or ibuprofen (800 mg TID). Approximately 73% of patients had osteoarthritis; 27% had rheumatoid arthritis. Use of low-dose aspirin for cardiovascular prophylaxis was permitted.

The published report of the trial (JAMA 2000;284:1247-55) was limited to data obtained during the first six months of study participation, although about 35% of patients received nine months or more of treatment. According to published six-month data, the annualized absolute risk (AR) for the primary endpoint of confirmed complicated UGI events (GI bleeds, perforation, or gastric outlet obstruction) was 0.76% for celecoxib vs. 1.45% for the pooled NSAID group (RR 0.53; 95% CI 0.26-1.11; p=0.09), a non-significant difference. The difference in AR was significant when the subgroup of patients not taking aspirin was considered [0.44% for celecoxib vs. 1.27% for the pooled NSAID group (RR 0.35; 95% CI 0.14-0.98; p=0.04)]. However, there was neither a significant difference nor a discernible trend in patients taking aspirin [2.01% for celecoxib vs. 2.12% for the pooled NSAID group (RR 0.95; 95% CI not calculated; p=0.49)], a result that raises the possibility that COX-2 inhibitors may not provide a clinically relevant GI protective effect for patients on low dose aspirin.

When the entire study period was considered, there was no significant difference between celecoxib and the pooled NSAID group for the primary endpoint of confirmed complicated UGI events in the overall study population, the subgroup of patients not receiving aspirin, or the subgroup of patients receiving aspirin. The differences in statistical significance between six-month data and data from the entire study period appeared to be due to the occurrence of relatively more confirmed complicated UGI events in the celecoxib group than in NSAID groups subsequent to the first six months (see table below).

Number of confirmed complicated UGI events in the CLASS trial
(uncensored intent-to-treat data)

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
First 6 months	11	9	11
Entire Study Period	17	10	11

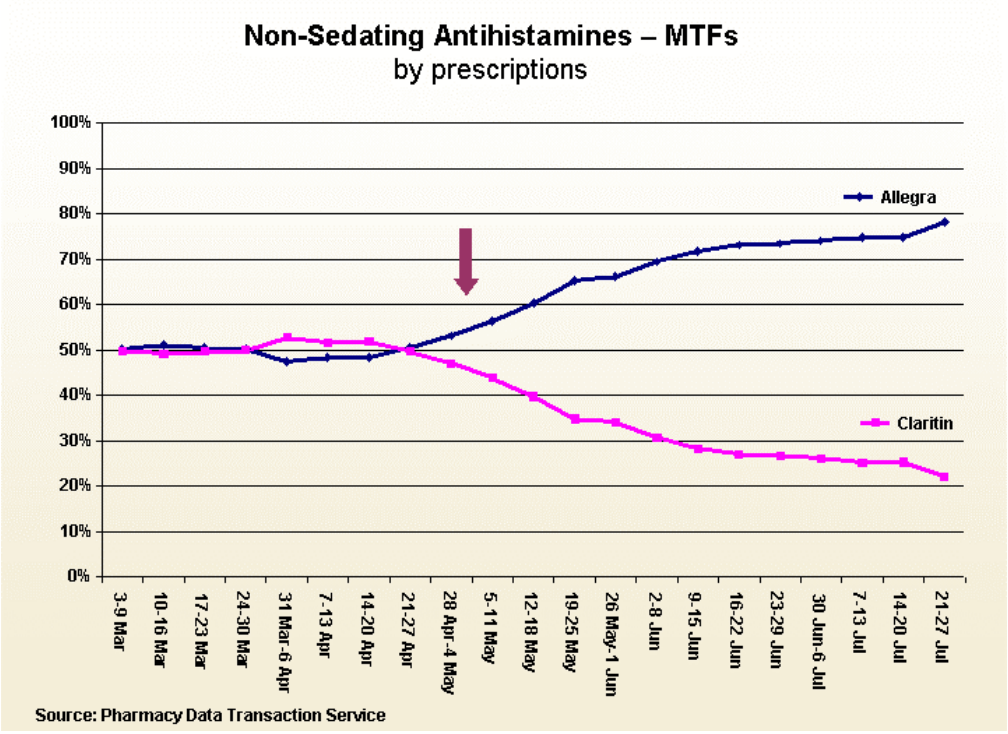
Adapted from Tables 13 and 14, Medical Officer Review for Celebrex®, available at:
www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc

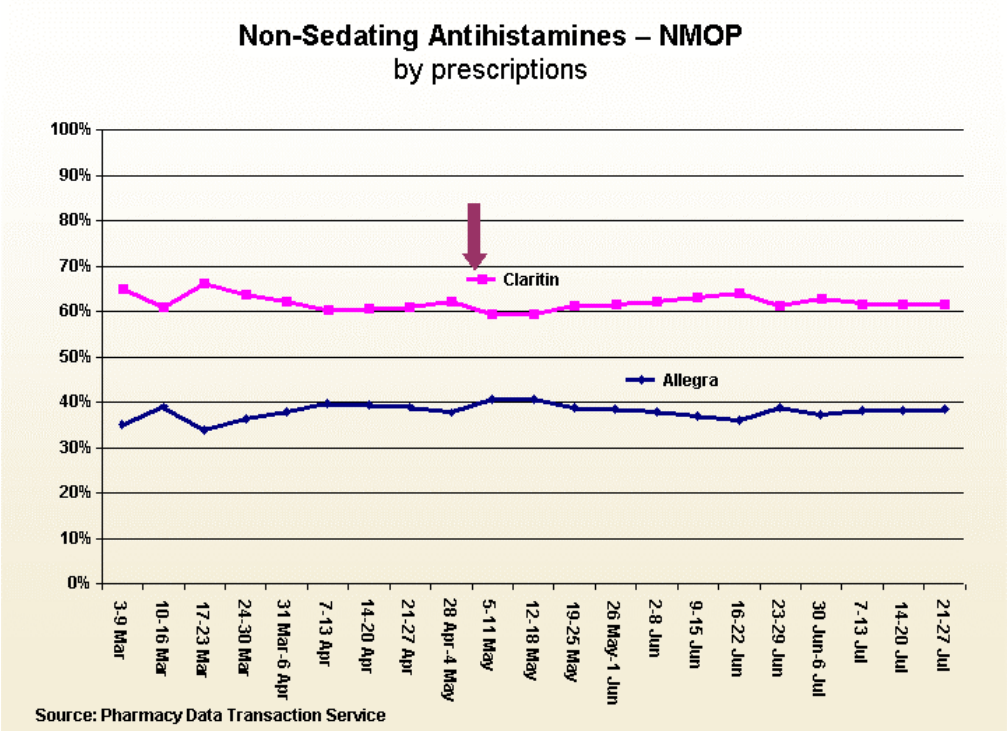
The manufacturer has suggested that this is primarily due to disproportionate dropouts secondary to GI symptoms (e.g., dyspepsia) among patients receiving comparator NSAIDs, artificially decreasing the number of patients in the NSAID group susceptible to GI adverse events. FDA reviewers raise a number of questions concerning the validity of this explanation.

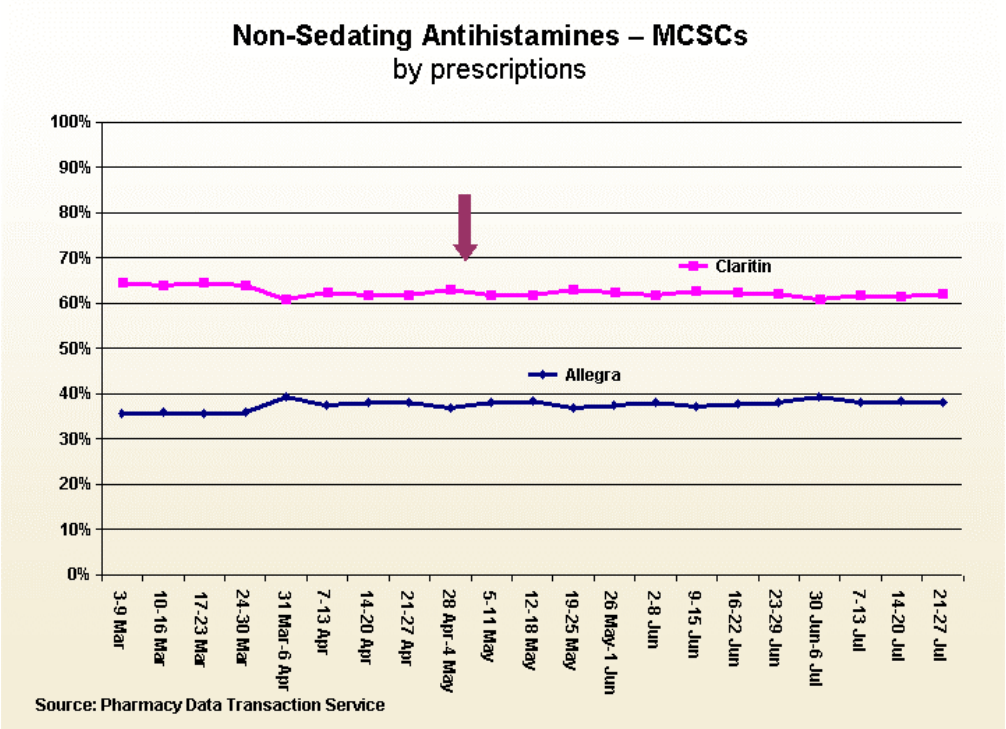
FDA briefing documents and reviews also provide separate data for the two comparator NSAIDs. All differences that were statistically significant between celecoxib and pooled NSAIDs were significant for celecoxib versus ibuprofen. The differences between celecoxib and diclofenac were not statistically significant for any of the endpoints.

FDA briefing documents and reviews are available at *www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm*.

Appendix C: Market Share and Cost Graphs for the Non-Sedating Antihistamines






Non-Sedating Antihistamines – MCSCs
by prescriptions
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Claritin
Allegra
3-9 Mar
10-16 Mar
17-23 Mar
24-30 Mar
31 Mar-6 Apr
7-13 Apr
14-20 Apr
21-27 Apr
28 Apr-4 May
5-11 May
12-18 May
19-25 May
26 May-1 Jun
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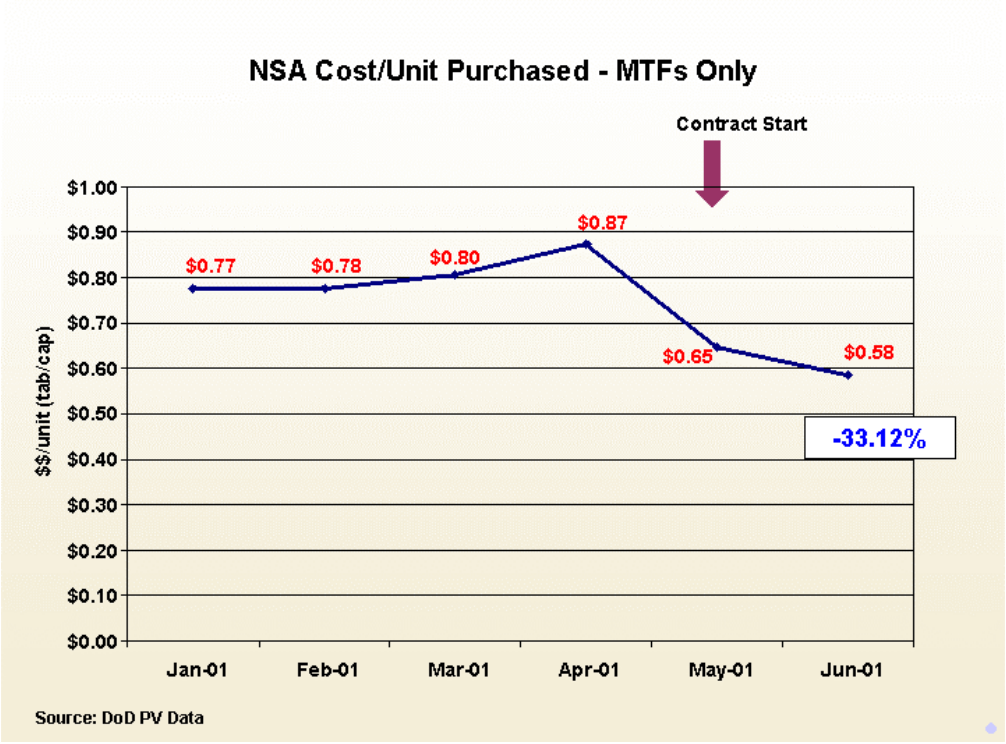

NSA Cost/Unit Purchased - MTFs Only
Contract Start
$1.00
$0.90
$0.80
$0.70
$0.60
$0.50
$0.40
$0.30
$0.20
$0.10
$0.00
$$/unit (tab/cap)
$0.77
$0.78
$0.80
$0.87
$0.65
$0.58
-33.12%
Jan-01
Feb-01
Mar-01
Apr-01
May-01
Jun-01
Source: DoD PV Data

Department of Defense
Pharmacoeconomic Center

1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE **7 JUNE 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0900 hours on 7 June 2001, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Bill Sykora, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
CAPT Chuck Bruner	Coast Guard
Dick Rooney	Department of Veterans Affairs
LtCol Greg Russie, BSC	Joint Readiness Clinical Advisory Board
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Ray Nan Berry	Health Net Federal Services
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)

MEMBERS ABSENT

COL John R. Downs, MC	Air Force

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
COL Ardis Meier, BSC	Air Force Pharmacy Consultant
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CAPT Pat Welter, MSC	Navy Bureau of Medicine & Surgery
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
David Chicoine	Uniformed Services Family Health Plan
Bill Chamberlain	Defense Supply Center Philadelphia
Mark Petruzzi	Merck-Medco
Shannon Rogers	Merck-Medco
Elizabeth Scaturro	Merck-Medco
Shana Trice	DoD Pharmacoeconomic Center
Vinnie Valinotti	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Gina Wu	Merck-Medco

3. **ADMINISTRATIVE ISSUES** – The minutes from the last meeting were accepted as written.

4. **REPORT FROM THE DOD EXECUTIVE COUNCIL MEETING** – COL Remund reviewed materials presented at the Executive Council Meeting concerning utilization and cost trends for drugs in the top six classes (by dollar expenditure) in DoD Military Treatment Facilities (MTFs) and the National Mail Order Pharmacy Program (NMOP). COL Remund also informed the committee about the award, contract provisions, and implementation of the joint VA/DoD national pharmaceutical contract for non-sedating antihistamines.

5. **IMPLEMENTATION OF FY 00 AND FY 01 NATIONAL DEFENSE AUTHORIZATION ACTS** – COL Davies briefed the Committee on the ongoing efforts to implement the pharmacy benefit provisions of the FY 00 and FY 01 National Defense Authorization Acts.

6. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status; NMOP or retail network formulary restrictions (quantity limits or prior authorization); and the Basic Core Formulary (BCF) status for 11 new drugs (see Appendix A). Additional discussion concerning the following drugs is also summarized in Appendix A: insulin glargine (Lantus; Aventis), PEG-interferon alfa 2b (PEG Intron; Schering), fluticasone/salmeterol powder for inhalation (Advair Diskus; Glaxo SmithKline), fluoxetine 90-mg capsules (Prozac Weekly; Lilly), and imatinib mesylate (Gleevec; Novartis).

7. **NON-PREFERRED/PREFERRED DRUG PAIRS IN THE NMOP** – MAJ Mickey Bellemin and Paul Vasquez (DSCP) reported that on 1 April the NMOP contractor, Merck-Medco, ceased making calls to physicians concerning all non-preferred/preferred drug pairs in the NMOP Preferred Drug Program except diltiazem. DSCP and Merck-Medco agreed to this change in order to accommodate the increased NMOP workload from the expansion of the pharmacy benefit to all beneficiaries over 65 years of age. Phone calls for diltiazem will continue because of the national contract for diltiazem extended release (Tiazac) and the high cost avoidance per attempted provider contact associated with this non-preferred/preferred drug pair.

CAPT Joe Torkildson reported a $2.8 million cumulative cost avoidance over the 22-month duration of the NMOP Preferred Drug Program (see Appendix B). COL Remund commented that the committee should continue to monitor market shares in classes in which a non-preferred/preferred drug pair existed in order to assess the true effect of these interventions and the potential effect of similar interventions in the future.

8. PRIOR AUTHORIZATIONS

A. *Cost avoidance from NMOP prior authorizations (PAs)* – Shana Trice (PEC) reported on the estimated cost avoidance due to PAs in the NMOP. The cost avoidance per prescription is based on the cost avoidance model that was outlined in the Aug 00 DoD P&T Committee minutes.

PA Cost Avoidance per New Prescription Submitted to the NMOP*

Drug	3rd Quarter FY 00	4th Quarter FY 00	1st Quarter FY 01	2nd Quarter FY 01
Sildenafil	$13.60	$26.46	Not calculated**	Not calculated**
COX-2 inhibitors	$11.66	$18.56	$10.95	$8.74
Etanercept	$327.20	$111.86	$7.89	$76.96

* Cost avoidance due to the PA for antifungals for onychomycosis (ciclopirox, itraconazole, terbinafine) is not calculated using this model because the PA differs substantially from the other PAs. Unlike the other PAs, which authorize dispensing of new and refill prescriptions for a year, each course of therapy with antifungal medications for the treatment of onychomycosis goes through the PA process.

** The PEC is working with Merck Medco and DSCP to revise the PA cost avoidance model to account for prior authorization of refill prescriptions.

- *Etanercept* – The progressive decline in the cost avoidance for the etanercept PA in the NMOP noted at the last meeting appears to have reversed (see table). However, considering the high cost of etanercept, the low number of prescriptions, and the even lower number of prescriptions that go through the PA process, the analysis is likely to be extremely sensitive to small changes in the number of prescriptions that are not filled because they do not meet PA criteria. The analysis of cost avoidance due to the etanercept PA in the retail network discussed at the last meeting has not yet been completed. The committee did not take any action concerning the etanercept PA.

B. *Temporary lapse in the NMOP PA program* – Paul Vasquez (DSCP) reported that the NMOP PA program was suspended from mid April 01 to early May 01 to accommodate large increases in NMOP workload due to the expansion of the pharmacy benefit to all beneficiaries over 65 years of age.

C. *Utilization of the NMOP and retail network pharmacies for drugs subject to PA* – The committee discussed the possibility of using data from the Pharmacy Data Transaction Service (PDTS) to analyze the extent to which patients who are denied prescriptions for COX-2 inhibitors in the NMOP subsequently fill these prescriptions at retail network pharmacies. The COX-2 inhibitor PA was withdrawn in the retail network in Aug 00 because federal regulations governing TRICARE currently allow prior authorizations to be applied in the retail pharmacy

networks only for clinical considerations (appropriateness of therapy), and not for cost-effectiveness considerations.

Bill Hudson (Humana) presented longitudinal data concerning utilization and costs of COX-2 inhibitors, brand name nonsteroidal anti-inflammatory drugs (NSAIDs) and generic NSAIDs in Regions 3 and 4. He reported that utilization of COX-2 inhibitors, which had decreased when the COX-2 inhibitor PA had been put into place, essentially doubled when the COX-2 inhibitor PA was discontinued.

The number of patients who opt to fill COX-2 inhibitor prescriptions in retail network pharmacies instead of the NMOP due to the presence of the COX-2 inhibitor PA is unknown. Prescriptions filled at the NMOP are less costly to DoD than those filled in the retail network. In addition, it is likely that some patients who opt to fill one prescription in the retail network rather than the NMOP will decide to fill all their prescriptions in the retail network. The committee requested that the PEC utilize data from PDTS to analyze the shift of patients from NMOP to the retail network.

C. *Antifungals for onychomycosis* – Ciclopirox topical solution (Penlac Nail Lacquer) was added to the existing NMOP PA for antifungals for onychomycosis as of 10 May 01. No problems with NMOP implementation were reported.

Bill Hudson (Humana) expressed concern about combination therapy with oral antifungals and ciclopirox being prescribed by a small number of providers. It is doubtful that this combination increases the effectiveness of onychomycosis treatment by any clinically significant degree. Product labeling for ciclopirox recommends against concurrent therapy with oral antifungals since it is not known whether ciclopirox interferes with the action of the oral antifungals. Because ciclopirox requires regular visits to remove infected nail material, use of the combination not only increases medication cost but may also increase the total cost of therapy. The committee requested more information about the incidence of combination therapy.

D. *Revision of PA forms* – Changes to clinical rationale language for the COX-2 inhibitors due to the CLASS study are in progress. The committee requested that clinical rationale language for the antifungals for onychomycosis to be changed to reflect recent safety announcements by the Food and Drug Administration (FDA) concerning terbinafine and itraconazole.

9. STATUS OF LOW MOLECULAR WEIGHT HEPARINS (LMWHs) IN THE NMOP AND RETAIL NETWORK – CAPT Torkildson reported on the PEC's survey of providers concerning the necessity to have the LMWHs available through the NMOP. While most providers did not feel this to be necessary, the obstetricians surveyed agreed that their patients were prescribed LMWH therapy for a long enough period of time to make acquiring the drug from the NMOP a viable option. While the volume of prescriptions is expected to be low, the committee agreed that there is no reason to not have low molecular heparins designed for self-administration available through the NMOP for those patients who might benefit. The committee added LMWHs (dalteparin, enoxaparin, and tinzaparin) to the NMOP formulary. The low molecular weight heparinoid, danaparoid, was not added because it is indicated for intravenous administration only and is unlikely to be administered as an outpatient medication.

10. REVIEW OF INJECTABLE MEDICATIONS AVAILABLE THROUGH THE NMOP - The committee clarified that the potential for self-administration is only one of the factors for considering drugs for the NMOP Covered Injectables List. Other factors include the feasibility of

dispensing the medications through mail order (Merck-Medco's mail order facilities are not set up to handle sterile compounding of parenteral products) and the relative likelihood that the medications will be needed on an outpatient basis.

One of the MCSC pharmacy directors requested removal of Zoladex from the NMOP Covered Injectables list, since it is an implant that requires an office visit and insertion under sterile conditions. It was pointed out that Lupron, although administered as an intramuscular injection rather than implanted subcutaneously, is in most cases also not suitable for self-administration. The committee requested the PEC to review the NMOP Covered Injectables list to identify items not designed for self-administration or commonly used in an outpatient setting and review the current utilization of these medications through the NMOP. The committee did not change the availability of Zoladex through the NMOP at this time, pending results of the review.

11. **CONTROLLED DISTRIBUTION OF ETANERCEPT (ENBREL) –** Since MTF pharmacies, unlike retail pharmacies, are not required to submit patient enrollment numbers to obtain etanercept, DoD beneficiaries can obtain etanercept from MTF pharmacies even if they did not enroll with Immunex. However, unenrolled patients may experience problems if they need to obtain etanercept from a source other than an MTF pharmacy. A process has been established for patients not enrolled with the manufacturer who have been receiving etanercept from a MTF and who wish to obtain their medication through the retail network, or who have separated from the military, to obtain enrollment numbers and receive etanercept through the NMOP or a retail network pharmacy. Patients who have not previously received etanercept (new starts) are subject to the same waiting list procedures as civilian patients. LTC De Groff reported that a letter addressing these procedures has been sent to the field by the pharmacy consultants/specialty leaders. A copy of the letter is available as Appendix D.

12. **CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN) –** Because of specialized educational requirements mandated by the FDA, dofetilide is only available for outpatient use through Stadtlander's Pharmacy/CVS Procare (which is a non-network pharmacy for DoD beneficiaries). COL Davies reported that the biggest problem is that prime patients are being forced to pay the copay for a non-network pharmacy. He reported that there is a potential for developing a new payment mechanism to handle not just dofetilide, but also the increasing number of drugs with unique distribution systems. Efforts to establish such a payment mechanism are in progress.

13. **ADJOURNMENT –** The meeting adjourned at 1400 hours. The next meeting will be held at Ft Sam Houston, TX and is tentatively scheduled for 16 Aug 01 at 0800. All agenda items should be submitted to the co-chairs no later than 20 Jul 01.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NATIONAL MAIL ORDER PHARMACY FORMULARY AND DOD BASIC CORE FORMULARY

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP or retail network formulary restrictions	BCF Status
Ziprasidone capsules (Geodon; Pfizer)	5 Feb 01; atypical antipsychotic for the treatment of schizophrenia. Labeling for ziprasidone specifically notes that: "When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs." It is not known whether ziprasidone will cause torsade de pointes.	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** antipsychotics: haloperidol oral; no atypical antipsychotics
Galantamine tablets (Reminyl; Johnson & Johnson)	23 Feb 01; acetylcholinesterase inhibitor; indicated for the treatment of mild to moderate dementia of Alzheimer's disease	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class**: None
Bimatoprost ophthalmic solution, 0.03% (Lumigan; Allergan)	16 Mar 01; synthetic prostamide (prostaglandin analog); indicated for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension; should be used in patients who cannot tolerate or have failed treatment with other IOP-lowering medications	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** Ophthalmic agents for glaucoma: timolol, brimonidine, and pilocarpine ophthalmic solutions; no prostaglandin analogs
Travoprost ophthalmic solution, 0.004% (Travatan; Alcon)	16 Mar 01; synthetic prostaglandin analog; indicated for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension; should be used in patients who cannot tolerate or have failed treatment with other IOP-lowering medications	Added to NMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** Ophthalmic agents for glaucoma: timolol, brimonidine, and pilocarpine ophthalmic solutions; no prostaglandin analogs

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP or retail network formulary restrictions	BCF Status
Insulin glargine [rDNA origin] injection (Lantus; Aventis)	20 Apr 00 (launched 21 May 01); long-acting (basal) insulin; indicated for once daily SQ administration at bedtime for treating adult and pediatric patients with type 1 diabetes mellitus, or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. **Note:** Insulin glargine is a clear solution that should not be mixed with other insulin products; use of insulin glargine does not eliminate the need for mealtime coverage.	Added to NMOP Formulary **Note**: The NMOP Covered Injectables list includes all forms of insulin and insulin analog products (i.e., Humalog)	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** Human insulin [rDNA origin} NPH, regular, 70/30 (Novolin brand only). There is a DoD/VA single source contract for the 10 mL bottles of these products (the contract also includes human lente insulin). The contract does not affect formulary status of other insulin products.
Comments about insulin glargine: The committee agreed that, while insulin glargine represents an advance in diabetes therapy and may be rapidly adopted by clinicians, it is too early to add it to the BCF. The PEC will monitor usage and will bring the item back to the committee for reconsideration if usage and demand for the product increase markedly and when clinicians have had a chance to become familiar with the product. The true potential advantage of basal insulin may only be realized when intranasal insulin becomes available, since this combination may allow even insulin dependent diabetics to limit subcutaneous injections to one daily.				
PEG-interferon alfa-2b powder for SC injection (PEG-Intron; Schering)	19 Jan 01; interferon product; indicated as once-weekly monotherapy of chronic hepatitis C in patients not previously treated with interferon alpha who have compensated liver disease, and who are at least 18 years old	Added to the NMOP Formulary **Note**: Interferon alfa products (Infergen, Roferon-A, Intron A) and combination interferon alfa/ribavirin (Rebetron) are on NMOP Covered Injectables list	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** None
Comments about Hepatitis C treatment: The VA representative, Mr. Dick Rooney, reported on the VA Chicago Health System's protocol for treatment of hepatitis C with ribavirin/interferon alfa 2b (Rebetron). Approximately 70% of patient with hepatitis C in North America are infected with genotype 1, which is less likely to respond to interferon treatment than genotypes 2 or 3. The VA performs a genotype test (which costs approximately $70) after the patient and provider have reached intention to treat. Patients with genotype 1 are then treated for one year, compared to six months for other genotypes. This both prevents unnecessary exposure to treatment that is unlikely to result in benefit and is cost-effective (cost savings of approximately $15,800 per 10 patients tested, not including avoidance of drug side effects and reduced provider visits and laboratory monitoring).				

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP or retail network formulary restrictions	BCF Status
Fluticasone / salmeterol powder for inhalation **100/50, 250/50, and 500/50 mcg per inhalation** (Advair Diskus; Glaxo SmithKline)	18 Aug 00; combination product containing an oral inhaled corticosteroid and a long-acting beta agonist; indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 12 years of age and older. Advair is not indicated for the relief of acute bronchospasm.	Added to NMOP Formulary	**Quantity Limits** 1 inhaler (60 blisters) per 30 days (retail), 3 inhalers (180 blisters) per 90 days (NMOP) **Prior Authorization** No	Not added to BCF **BCF drugs in this class:** No other oral inhaled corticosteroid/beta agonist combination products exist; both fluticasone and salmeterol oral inhalers are on the BCF
Comments about fluticasone/salmeterol oral inhaler: The committee agreed that there is no evidence to support a clinically significant advantage (in terms of improved safety or efficacy) for the combination product compared to the two component products given separately. The combination product may be more convenient than two individual inhalers and may result in better compliance with therapy. On the other hand, the fixed dose combinations may make titration (including temporary increases in fluticasone dose during peak seasons, respiratory infections, etc.) more difficult. Advair is a dry powder Diskus device, which is substantially different from metered dose inhaler devices. Most use of fluticasone products in DoD is for the metered dose inhaled product, with minimal use of the currently available Flovent Diskus device. There is no price advantage to Advair compared to fluticasone and salmeterol given separately, although there may be cost efficiencies to MTF pharmacies (fewer prescriptions to fill) and patients (one less copay at NMOP or retail). Patent protection on fluticasone, the oral inhaled corticosteroid with the largest market share in DoD, is expected to expire in the latter part of 2003, although an "A-rated" generically substitutable product is unlikely due to environmental restrictions on production of chlorofluorocarbons (CFCs). The committee decided not to add this combination product to the BCF. The PEC will continue to monitor usage in this rapidly changing drug class.				
Formoterol fumarate powder for inhalation (Foradil; Novartis)	16 Feb 01; long-acting beta agonist; indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta2-agonists. It is not indicated for patients whose asthma can be managed by occasional use of a short-acting beta2-agonist. **Note:** formoterol has a more rapid onset of action than salmeterol (2-3 minutes vs. 10-15 minutes), previously the only available long-acting oral inhaled beta agonist. However, it is NOT a substitute for albuterol as a quick-relief medication.	Added to NMOP Formulary	**Quantity Limits** 1 inhaler (60 capsules) per 30 days (retail), 3 inhalers (180 capsules) per 90 days (NMOP) **Prior Authorization** No	Not added to the BCF **BCF drugs in this class:** salmeterol oral inhaler

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP or retail network formulary restrictions	BCF Status
Fluoxetine HCl 90-mg capsule (Prozac Weekly; Lilly)	26 Feb 01; selective serotonin reuptake inhibitor; indicated for the maintenance treatment of depression after an initial antidepressant response is obtained with once daily fluoxetine	Added to NMOP Formulary	**Quantity Limits** 4 capsules (one blister pack) per 30 days (retail); 12 capsules (3 blister packs) per 90 days (NMOP) **Prior Authorization** No	Excluded from BCF listing for fluoxetine. MTFs are not required to add Prozac Weekly to their formularies, but may do so if they so desire. **BCF drugs in this class:** citalopram, fluoxetine (excludes Sarafem), paroxetine, sertraline
Comments about fluoxetine 90-mg once-weekly capsule: Weekly administration of fluoxetine may represent a convenience advantage over once daily dosing, although this remains to be proven. The implications of once weekly dosing of medications for patient adherence to therapy are unknown. Plasma concentrations fluctuate to a much greater degree with once weekly dosing; the effect of patients missing once weekly doses or taking them a few days late may effectively equate to interruptions in therapy, even with the long half-life of fluoxetine. The pharmacokinetic effects, clinical consequences, and adverse effects associated with once weekly doses greater than 90 mg are unknown. The 90-mg capsule appears to be associated with more diarrhea than the 20-mg capsule, despite its delayed release formulation. The weekly formulation does not appear to be any more effective, and may be less effective, than once daily dosing. It is indicated only for maintenance treatment of depression. Prozac Weekly 90 mg once weekly costs less per month than Prozac 20 mg once daily. However, impending generic availability of fluoxetine (expected in Aug 01) and anticipated price decreases render this cost difference irrelevant, even without considering the uncertain clinical utility of this formulation of fluoxetine.				
Esomepra-zole (Nexium; AstraZeneca)	20 Feb 01; proton pump inhibitor (PPI); indicated for 1) short-term healing of confirmed erosive esophagits; 2) maintenance of healing of erosive esophagitis; 3) treatment of symptomatic gastroesophageal reflux disease (GERD); and 4) combination therapy with clarithromycin and amoxicillin for the eradication of Helicobacter pylori in patients with duodenal ulcer disease or a history of duodenal ulcer disease	Excluded from the NMOP Formulary as a non-contract drug. Prescriptions for esome-prazole may be filled through the NMOP only if documented medical necessity is established.	**Quantity Limits** General rule applies **Prior Authorization** No	Not added to the BCF. The PPI drug class is closed on the BCF. MTFs are required to have the contract agent (omeprazole) on their formularies and may not have any non-contract PPIs, including esomeprazole, on their formularies. Prescriptions for esomeprazole may be filled at MTFs only if documented medical necessity is established. **BCF drugs in this class:** omeprazole

Generic name (Trade name; manufacturer)	FDA approval date, drug class, FDA-approved indication	NMOP Formulary Status	NMOP or retail network formulary restrictions	BCF Status
Imatinib mesylate (Gleevec; Novartis)	10 May 01 (accelerated approval); protein-tyrosine kinase inhibitor (new drug class); oral once daily medication with a relatively favorable adverse effect profile; indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy	Added to the NMOP Formulary	**Quantity Limits** Limited to 45 days supply in the NMOP; general rule applies in the retail network **Prior Authorization** No, monitor usage	Not added to the BCF **BCF drugs in this class:** None (there are no other drugs in this class). The only antineoplastic agents on the BCF are tamoxifen and methotrexate.

Comments about imatinib mesylate: This drug is an entirely novel antineoplastic agent. Imatinib inhibits the abnormal protein-tyrosine kinase that results from the Bcr-Abl gene rearrangement characteristic of chronic myelogenous leukemia (CML). This mechanism of action suggests that it would only be active against tumors that express this abnormal protein; however, it also has some activity against other protein-tyrosine kinases, some of which are constitutively expressed by other tumor types. It is currently approved only for use in CML; its use should be confined to those patients who are Philadelphia chromosome positive, since this indicates the presence of the Bcr-Abl gene.

Imatinib also has activity against the c-kit protein-tyrosine kinase that is constitutively expressed in at least 70% of small cell lung cancers and in virtually all gastrointestinal stromal tumors. *In vitro* studies have suggested that imatinib may have activity against small cell lung cancer, while a recent case report described a patient with a gastrointestinal stromal tumor who experienced a good partial response to therapy following treatment with imatinib that was maintained for at least 11 months. Imatinib has also demonstrated activity against the protein-tyrosine kinase activated by platelet-derived growth factor (PDGF) receptor that is activated abnormally in many brain tumors, No data are currently available that suggest efficacy in treating this condition. Animal studies suggest that imatinib may decrease the rate of restenosis of coronary arteries following angioplasty due to its inhibition of the protein-tyrosine kinase that is normally activated by PDGF following this procedure. There are therefore several additional conditions for which there are very limited data suggesting the possibility of benefit.

Imatinib capsules are dosed once daily, and are relatively well tolerated in comparison to other chemotherapeutic regimens. The monthly cost of therapy based on FSS prices ranges from approximately $1,500 (chronic CML) to $2,200 (treatment of CML in accelerated phase or blast crisis). Because of the limited scope of the available published clinical trials, the optimal duration of treatment remains undefined.

Members of the committee expressed concern over several factors that increase the potential for this product to be used for other than FDA approved indications. These include: the publicity in the lay press surrounding imatinib's release, the possibility that this drug may have efficacy in other malignancies, and the pressure from patients with other malignancies who have failed conventional therapy and have few or no remaining alternatives for treatment. 32 CFR 199.4(g)(15) states in part: "CHAMPUS can also consider coverage of unlabeled or off-label uses of drugs that are Food and Drug Administration (FDA) approved drugs that are used for indications or treatments not included in the approved labeling. Approval for reimbursement of unlabeled or off-label uses requires review for medical necessity, and also requires demonstrations from medical literature, national organizations, or technology assessment bodies that the unlabeled or off-label used of the drug is safe, effective and in accordance with nationally accepted standards of practice in the medical community."

Concern was also expressed that unmonitored use of imatinib might result in a delay in appreciating its value in treating other conditions. The committee discussed the possibility of instituting a prior authorization for this medication in the NMOP and retail network in order to minimize inappropriate use while allowing identification of additional indications. The proposed wording of the requirement for authorization was stated as, "treatment of an FDA-approved indication, or enrollment in an NCI-approved clinical trial". However, the committee was then reminded that 32 CFR 199.4 also excludes coverage for "services and supplies provided as a part of or under a scientific or medical study, grant, or research program." It was pointed out that the lack of a prior authorization does not prevent MCSC Utilization Management Programs from ensuring that prescribed therapy complies with TRICARE rules. The Committee appreciated that strict application of TRICARE rules will likely engender strong objections from patients and prescribers in this situation. Also, with over 350 new oncology drugs currently undergoing clinical trials, it was understood that this question would likely surface repeatedly in the future. The Committee felt that input from a higher level within TMA would be valuable in assisting them in determining how best to deal with this issue.

The committee approved placing imatinib on the NMOP formulary without a requirement for prior authorization. A quantity limit of a 45-day supply was established to minimize waste without overly burdening patients. Without a PA, the NMOP will not collect data on diagnoses of patients prescribed the drug. The PEC will monitor usage and report at the next meeting.

APPENDIX B: CUMULATIVE SUMMARY OF COST AVOIDANCE ASSOCIATED WITH THE NATIONAL MAIL ORDER PHARMACY (NMOP) PREFERRED DRUG PROGRAM

Program Summary

- Program started in June 1999 with 8 preferred/non-preferred groups and ended 31 Mar 01 as a result of increased prescription volume related to expansion of the DoD pharmacy benefit to allow all DoD beneficiaries 65 years of age or older access to the NMOP and retail network. Calls will continue for diltiazem due to the existence of the national contract for Adalat CC.
- During these 22 months, the program resulted in a total cost-avoidance of $2,841,647. A total of 31,574 attempted prescriber contacts were made to request switches from non-preferred drugs to preferred alternatives. The estimated cost-avoidance per attempted provider contact was $90.

Cumulative Table: Summary of Switch Rates and Estimated Cost Avoidances Jun 99 – Mar 01*

Non-Preferred Drug	Preferred Drug	Switch Rate	Estimated Cost Avoidance	Total Number of Attempted Provider Contacts*	Estimated Cost Avoidance per Attempted Provider Contact**	Annualized Estimated Cost Avoidance
Cardizem CD Dilacor XR, Diltia XT, Diltiazem XR	Tiazac	69%	$905,784	6392	$142	$494,064
Procardia XL[1]	Adalat CC	51%	$417,508	2097	$199	$227,732
Lodine XL, Relafen, Voltaren XR, DayPro, Naprelan	Generic NSAIDs	30%	$724,985	7791	$93	$395,446
H2 Blockers[2]	Generic Ranitidine	40%	$437,715	3749	$117	$238,754
Enalapril (Vasotec)[3]	Zestril	48%	$141,304	2741	$52	$77,075
Famvir, Valtrex[4]	Acyclovir	23%	$11,081	1670	$7	$6,044
Pletal[5]	Pentoxifylline	12%	$3,424	280	$12	$1,868
Ditropan XL, Detrol	Generic oxybutynin	29%	$199,846	6854	$29	$109,007
		Total	$2,841,647	31,574	$90	$1,549,990

* Assumes that each new prescription received for a non-preferred drug resulted in one attempted provider contact.

** Calculated as the total cost avoidance Oct 00 – Mar 01 divided by the total number of attempted provider contacts made for non-preferred drugs in this class during the same period.

1. Calls for Procardia XL diminished significantly (from 135 per month in Jun 00 to 7 per month in Dec 00), due to the introduction of generic equivalents for some strengths of Procardia XL. Calls for Procardia XL were discontinued as generic equivalents became available.
2. Implemented Dec 99
3 Implemented Feb 00. Vasotec was removed from the list of non-preferred drugs when a generic equivalent became available at a competitive price in Oct 00.
4. At the May 00 meeting, the committee changed the criteria for Famvir and Valtrex so that calls would be made only for prescriptions written for chronic use (> 30 day supply). This change took effect 1 July 00.
5. Implemented Feb 00. Removed from the list of non-preferred drugs at the Aug 00 meeting (effective Sep 00), due to a low switch rate.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. *Additions to the BCF*

      1) Fluocinonide 0.05% cream

   B. *Changes and clarifications to the BCF*

      1) The BCF listing for digoxin oral was changed to remove the specific brand designation for brand name Lanoxin.
      2) The BCF listing for doxycycline oral was clarified to exclude doxycycline 20-mg capsules (Periostat).
      3) The BCF listing for methylphenidate oral was clarified to exclude Metadate CD.
      4) The BCF listing for triamcinolone acetonide 0.1% topical was clarified to specify triamcinolone 0.1% cream.

2. **NMOP FORMULARY CHANGES**

   A. *Additions to the NMOP Formulary* (See Appendix A)

      1) Low Molecular Weight Heparins (dalteparin, enoxaparin, tinzaparin)
      2) Ziprasidone (Geodon; Pfizer)
      3) Galantamine (Reminyl; Johnson & Johnson)
      4) Bimatoprost ophthalmic solution, 0.03% (Lumigan; Allergan)
      5) Travoprost ophthalmic solution, 0.004% (Travatan; Alcon)
      6) Insulin glargine [rDNA origin] injection (Lantus; Aventis)
      7) PEG-interferon alfa-2b powder for SC injection (PEG-Intron; Schering)
      8) Fluticasone/salmeterol powder for inhalation (Advair Diskus; Glaxo SmithKline)
      9) Formoterol fumarate powder for inhalation (Foradil; Novartis)
      10) Fluoxetine hydrochloride 90-mg capsule (Prozac Weekly; Lilly)
      11) Imatinib mesylate (STI-571) (Gleevec; Novartis)

   B. *Exclusions from the NMOP Formulary*

      1) Esomeprazole (Nexium; Astra Zeneca)

   C. *Changes to the NMOP Preferred Drug Program*

      1) The NMOP Preferred Drug Program was discontinued 31 Mar 01. Calls requesting switches for non-contracted brands of diltiazem extended release (e.g., Cardizem CD, Dilacor XR, Diltia XT, Cartia XT, and generics) to the contract agent (Tiazac) will continue.

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK)**

   A. Fluticasone/salmeterol powder for inhalation (Advair Diskus; Glaxo SmithKline) - 1 inhaler (60 blisters) per 30 days (retail), 3 inhalers (180 blisters) per 90 days (NMOP)
   B. Formoterol fumarate powder for inhalation (Foradil; Novartis) - 1 inhaler (60 capsules) per 30 days (retail), 3 inhalers (180 capsules) per 90 days (NMOP)
   C. Fluoxetine hydrochloride 90-mg capsule (Prozac Weekly; Lilly) - 4 capsules (one blister pack) per 30 days (retail); 12 capsules (3 blister packs) per 90 days (NMOP)
   D. Imatinib mesylate (STI-571) (Gleevec; Novartis) - Limited to 45 days supply in the NMOP; general rule applies in the retail network

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK) –** None

APPENDIX D: ENBREL ENROLLMENT LETTER

ENBREL ENROLLMENT PROCESS

The following procedures should be used when dealing with patients on Enbrel (etanercept) in the Department of Defense medical treatment system. These procedures will remain in place until the DOD is notified by Immunex and/or Wyeth that they have changed. These procedures are based on current inventories of product.

1. Patients who were on Enbrel therapy before January 1, 2001 who enrolled in the Enbrel Enrollment Program and received a registration number will keep this number in the Immunex system. These patients will not be disenrolled by Immunex, although their number will remain "inactive" if they are receiving product through an MTF pharmacy or the NMOP mail order system. In some instances the NMOP system may require this number. If this is the case, Immunex will activate the number. This number will be used if the patient is receiving product through the retail pharmacy network program.

2. Patients who are receiving Enbrel therapy from a MTF pharmacy who are required to move for military or personal reasons (i.e. PCS, TDY assignments, relocations) and who prefer to continue to receive product from either an MTF pharmacy or the NMOP mail order system should notify the pharmacy from where they are moving. This pharmacy should contact Warren H. Yeager, R.Ph., National Account Manager-Federal Government, Wyeth-Ayerst Labs @ 1-888-685-5961 ext. 76924 and notify him of the new location of the patient. This will keep track of product at the different delivery systems throughout the DOD.

3. DOD patients who choose the retail pharmacy network option for obtaining Enbrel.

    - If these patients have already enrolled in the program and have a registration number and have been receiving product there will be no change in the process.

    - Because of the portability of the prescription in the DOD, if an Enbrel patient chooses to change from an MTF or NMOP to the retail option to have their script filled and does not have an enrollment number, the dispensing pharmacist will have to "opt out" of the confirmation process. The term "opt out" is recognized by the retail pharmacy network and is put in place to have the retail pharmacy contact HDS McKesson (1-888-436-2735) when this situation presents itself. HDS McKesson personnel are aware of this scenario. If the patient has an "inactive" number, this number will be activated by HDS McKesson and the patient will receive the medication. If the patient does not have a number, HDS McKesson will assign a number and the patient will receive the medication.

4. Patients who transfer from the DoD to the private sector due to separation.

    - Because these patients are already "accounted for" in the overall enrollment process they will be given an active enrollment number at the time of separation. The patient will need to call HDS McKesson @ 1-888-436-2735 and identify themselves as an existing patient transferring from DoD to the private sector due to release from Active military service. HDS McKesson will verify DoD eligibility and assign an enrollment number that will allow the patient to continue to receive the medication. HDS McKesson can verify the patient's DoD eligibility and medication history by calling the PDTS CSSC @ 1-800-600-9332, press #1, then select option #1 a second time.

5. Wait list procedures for adding new patients to the DOD program.

    - Patients will follow the same procedures as patients in the civilian community. They will need to call 1-888-436-2735(1-888-4ENBREL). They will be placed on the waiting list and given a "inactive" registration number.

Department of Defense
Pharmacoeconomic Center

1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE **6 June 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1215 hours on 6 June 2001 and from 0800 to 0900 hours on 7 Jun 2001, at the Uniformed Services University of the Health Sciences, Bethesda, MD. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
CAPT Chuck Bruner	Coast Guard
Dick Rooney	Department of Veterans Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LtCol Greg Russie, BSC	Joint Readiness Clinical Advisory Board representative

MEMBERS ABSENT

COL Bill Sykora, MC	Air Force
COL Rosa Stith, MC	Army

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TRICARE Management Activity
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
COL Ardis Meier, BSC	Air Force Pharmacy Consultant
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CAPT Pat Welter, MSC	Navy Bureau of Medicine & Surgery
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC (by teleconference)	DoD Pharmacoeconomic Center
LT David Hardy, MSC	TRICARE Management Activity
Angela Allerman (by teleconference)	DoD Pharmacoeconomic Center
Howard Altschwager	Deputy General Counsel, TRICARE Management Activity
Jonathan Blaker	TRICARE Management Activity
Bill Chamberlain	Defense Supply Center Philadelphia
Shana Trice	DoD Pharmacoeconomic Center
Vincent Valinotti	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING

The minutes were approved as written.

4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

All AMP funds remain "on hold" at TMA due to funding shortfalls in the Defense Health Program. If AMP funds are released, the PEC is prepared to provide usage and cost data to facilitate reimbursement of MTFs for expenditures on AMP drugs. Based on prime vendor data, MTFs spent $25,831,626 on AMP drugs during the first six months of FY 01 (see Appendix A).

5. REVIEW OF COX-2 INHIBITORS

The committee reviewed usage and cost data for COX-2 selective nonsteroidal anti-inflammatory drugs ("COX-2 inhibitors") and other nonsteroidal anti-inflammatory drugs (NSAIDs):

- Data from the Pharmacy Data Transaction Service from 1 Apr 01 to 25 May 01 indicated that market share for COX-2 inhibitors in MTFs has increased to 14% of all prescriptions for NSAIDs. Market shares for COX-2 inhibitors in the retail networks and the NMOP were 58% and 74% respectively (see table following).

	MTFs	MCSC retail network	NMOP
Number of prescriptions and percent of prescriptions for NSAIDs			
COX-2 inhibitors	56,822 (14%)	72,654 (58%)	25,525 (74%)
Traditional NSAIDs	345,621 (86%)	53,245 (42%)	8,853 (26%)
Total number of prescriptions for NSAIDs	402,443	125,899	34,378
Number of patients and percent of patients using NSAIDs			
COX-2 inhibitors	44,963 (13%)	54,151 (58%)	23,454 (75%)
Traditional NSAIDs	289,313 (87%)	39,946 (42%)	7,907 (25%)
Total number of patients using NSAIDs	334,276	94,097	31,361

Note: time period is 4/1/01 through 5/25/01; data from the Pharmacy Data Transaction Service Customer Service Support Center

- The PDTS data are consistent with data from the Uniformed Services Prescription Database (USPD), which indicated a 14% market share (by prescription volume) for COX-2 inhibitors at MTFs as of March 2001. TRICARE region market shares for COX-2 inhibitors ranged from less than 5% to more than 20%.
- According to prime vendor data, MTFs spent $19.1 million on NSAIDs during the first 6 months of FY 01, which is 84% more than the $10.4 million spent during the first 6 months of FY 00. The average unit cost of NSAIDs purchased by MTFs rose from $0.06 in October 98 to $0.22 in March 01.

The Council agreed that management of the COX-2 inhibitors should ideally focus on two issues:

- COX-2 inhibitor therapy should be targeted accurately and efficiently to those patients at greatest risk for GI adverse events
- DoD should reduce the unit cost of COX-2 inhibitors

DoD faces difficulty in trying to address these two issues simultaneously. A closed class contract that offers BCF status for a COX-2 inhibitor could possibly achieve a significant price reduction, but many MTFs do not want COX-2 inhibitors to be added to the BCF. These MTFs do not have a COX-2 inhibitor on their formularies because they do not have sufficient funding and/or they want to target therapy by using the non-formulary special order process to provide COX-2 inhibitors only to patients who are at greatest risk for GI adverse events. The Council agreed that:

- The PEC should continue data analysis and provide feedback to MTFs to assist them in targeting therapy
- MTFs should analyze utilization and cost of COX-2s at the local level
- The PEC should obtain feedback from MTFs concerning methods they use to target COX-2 therapy and the accuracy and efficiency of those methods.
- A contract for COX-2 inhibitors should be pursued only if there is a mechanism to target therapy to patients who are at greatest risk for GI adverse events.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

A. *Contract awards and renewals*

- The first joint DoD/VA closed class contract was awarded to Aventis Pharmaceuticals for the non-sedating antihistamine fexofenadine (Allegra) 60- and 180-mg tablets. The PEC previously issued implementation guidance for the non-sedating antihistamine contract (see Appendix B).
- DoD/VA single source contracts were awarded for the following drugs.
  - Ethinyl estradiol 35-mcg/norethindrone 1-mg tablets (Norinyl 1/35), 21s and 28s, to Watson Pharma
  - Norethindrone 35-mcg tablets (Nor-Q-D), 28s, to Watson Pharma
  - Ethinyl estradiol 35-mcg/1-mg ethynodiol diacetate (Demulen 1/35), 28s, to Pharmacia Corp.
  - Etodolac 200-, 300-mg capsules and 400-mg tablets, to Taro Pharmaceuticals
  - Hydrochlorothiazide 25-mg/50-mg tablets, to IVAX Pharmaceuticals (formerly Zenith-Goldline)
  - Prednisone 2.5-, 5-, 10-, 20-, and 50-mg tablets, to Pharmacia Corp.
  - Isosorbide mononitrate SA 30-, 60-, and 120-mg tablets, to Schwarz Pharma
  - Valproic Acid 250-mg capsules, to Sidmak Labs
  - Capsaicin 0.025% and 0.075% cream, to Qualitest Pharmaceuticals
  - Ticlopidine 250-mg tablets, to Par Pharmaceuticals
- As of 1 Jun 01, 44 joint VA/DoD national contracts have been awarded. Information on national pharmaceutical contracts, including NDC numbers and prices, is available on the DSCP website (www.dmmonline.com).

B. *Financial impact of contracts* – The estimated MTF cost avoidance due to national pharmaceutical contracts was $43.3 million for the first six months of FY 01. The $43.3 million in cost avoidance equals 7.9% of the $547.2 million that MTFs spent on pharmaceuticals through prime vendors during the first six months of FY 01. A summary of cost avoidance from national pharmaceutical contracts for FY 01 is provided in Appendix C.

C. *Report on Returned Goods Contract* – MAJ Cheryl Filby (DSCP) reported that, as of 5 June 01, 89 DoD facilities have signed up for the joint VA/DoD returned goods contract, which was awarded to Guaranteed Returns in Jan 01. More information on the Pharmaceutical Returns Management Program is available on the DSCP website at: http://dscp305.dscp.dla.mil/ dmmonline/pharm/return_program.asp

D. *Proton pump inhibitor contract* – Significant price reductions recently occurred in the proton pump inhibitor (PPI) market. Janssen lowered the FSS price of rabeprazole (Aciphex) to $0.22 per dose. In response to the market changes, the VA and TAP Pharmaceuticals have mutually agreed to cancel the VA's national contract for

lansoprazole (Prevacid) in favor of a BPA that sets the price for both strengths of lansoprazole at $0.55. Lansoprazole will remain on the VA National formulary, but the PPI class is now "open," so VA facilities may use other PPIs.

The DoD national contract price for omeprazole (Prilosec) is $1.09 per dose. The current option year expires on 30 Sep 01. The DoD P&T Executive Council strongly urges DSCP to negotiate a termination of the DoD national contract for omeprazole in a manner similar to what the VA negotiated.

E. *Potential contract for nasal corticosteroid inhalers* – The Council reiterated its support for establishing a joint VA/DoD closed class contract for a high potency aqueous nasal corticosteroid inhaler. Usage of nasal corticosteroid inhalers by pediatric patients should be taken into account in the contracting initiative.

F. *Potential contract for low molecular weight heparins/heparinoids (LMWHs)* — A closed class contract for a single LMWH for the outpatient treatment and prophylaxis of deep venous thrombosis (DVT) has been proposed. The Council assessed the therapeutic interchangeability of enoxaparin (Lovenox) and dalteparin (Fragmin) for outpatient treatment of DVT and prophylaxis of DVT and/or pulmonary embolism (PE) following hip or knee replacement surgery.

1) *Safety/Tolerability*

- Potential tolerability differences between the products are typically related to issues of administration (e.g., available syringe sizes) and are expected to be of relatively minor importance.
- The most important complication of anticoagulant therapy is bleeding. In a single head-to-head trial for prophylaxis of DVT following surgical repair of hip fracture, the incidence of major bleeding was 1/66 (1.5%) for dalteparin and 2/66 (3.0%) for enoxaparin. This was a small pilot study and may not represent the true incidence of major bleeding with either drug.
- Meta-analyses have found no significant difference between major bleeding rates with LMWHs and UFH, although differences have been reported in individual trials. In large clinical trials, major bleeding rates with UFH ranged from 0 to 7%, compared to 0 to 3% for LMWHs. It is difficult to draw any conclusion about the relative propensities of enoxaparin versus dalteparin to cause bleeding because of the lack of head-to-head data, differences in patient populations, dosing and regimen differences, and differences in how bleeding was defined across clinical trials.
- Enoxaparin and dalteparin are Pregnancy Category B and, unlike warfarin, are generally considered to be safe in pregnant patients requiring anticoagulation. According to case reports, patients with contraindications to warfarin have tolerated long-term use of dalteparin (2 months to 10 years) and enoxaparin (3 to 6 months).

2) *Efficacy for Outpatient Treatment of DVT*

- Enoxaparin is approved by the FDA for outpatient and inpatient treatment of DVT. Dalteparin is not approved by the FDA for treatment of either outpatient or inpatient treatment of DVT.
- There are no head-to-head trials comparing enoxaparin with dalteparin for treatment of DVT in either the inpatient or outpatient setting.
- *Enoxaparin vs. UFH* – Three large, well-conducted trials (two in the inpatient and one in the outpatient setting) compared enoxaparin with UFH for the treatment of DVT in a total of 917 patients. One trial also included patients with PE. No significant difference was noted in recurrent DVT/PE in the outpatient trial: enoxaparin 13/247 (5.3%); UFH, 17/254 (6.7%). However, only 33% of screened patients were considered eligible for study enrollment, and the studied population was generally at low risk for bleeding and did not have co-morbidities.
- *Dalteparin vs. UFH* – There are 11 published trials with dalteparin (seven in the inpatient and four in the outpatient setting) in a total of 1538 patients. However, while inpatient trials compared dalteparin with UFH, outpatient trials with dalteparin have not included an UFH comparison group. In a large (n=434), nonrandomized trial of dalteparin for the outpatient treatment of DVT, there were 7 cases of recurrent DVT (1.6%). These patients were considered to be at relatively low risk for bleeding and recurrent DVT/PE.
- Although most trials compared either dalteparin or enoxaparin to UFH, dalteparin trials were generally smaller and sometimes included patients with distal (calf vein) as well as proximal DVT (proximal DVT has a higher complication rate). Trials with enoxaparin primarily enrolled patients with proximal DVT. In addition, some of the dalteparin trials used surrogate efficacy measures (such as changes in thrombus size pre- and post-treatment) instead of clinical endpoints (such as incidence of recurrent DVT/PE). Comparison of the efficacy of the two drugs for outpatient treatment is further complicated by differences in patient populations (e.g., inclusion of patients with co-morbidities such as cancer, who are at increased risk for DVT/PE) resulting from differences in how patients were considered eligible for outpatient treatment.

3) *Efficacy for Prophylaxis of DVT Following Hip Replacement Surgery*

- Both enoxaparin and dalteparin are FDA-approved for DVT prophylaxis following hip replacement surgery.
- There are no head-to-head trials comparing enoxaparin with dalteparin in hip replacement surgery. Two trials compared dalteparin with warfarin and one trial compared enoxaparin with warfarin following hip replacement surgery. The incidence of symptomatic DVT/PE was lower with the LMWH than with warfarin in all three trials. There is insufficient evidence to conclude that enoxaparin and dalteparin differ significantly in efficacy for DVT prophylaxis following hip replacement surgery.

4) *Efficacy for Prophylaxis of DVT Following Knee Replacement Surgery*

- Of the two drugs, only enoxaparin is FDA-approved for DVT prophylaxis following knee replacement surgery.
- There are no head-to-head trials of enoxaparin and dalteparin for DVT prophylaxis. One double-blinded trial comparing enoxaparin and warfarin for DVT/PE prophylaxis following total knee replacement showed significantly fewer recurrent DVTs with enoxaparin compared to warfarin. There are no published trials that assess the efficacy of dalteparin for this indication.

5) *Other Factors*

- Enoxaparin is available as prefilled syringes in a wide range of dosages, which is an advantage for outpatient use. Dalteparin has only been available in pre-filled syringes in two dosages (2500- and 5000-U per 0.2 mL) and in a 10,000 U/mL multidose vial. Neither the prefilled syringes nor the multidose vial are optimal for the higher doses used for DVT treatment, which may require multiple injections. The manufacturer of dalteparin anticipates introduction of a higher concentration multidose vial and 7500- and 10,000-U prefilled syringes.
- Articles in the pharmacy literature report on at least two health systems that have changed from enoxaparin to dalteparin using a therapeutic interchange program. The program at one institution includes only DVT treatment and prophylaxis. Patients receiving enoxaparin for knee replacement surgery and cardiology indications are excluded. A preliminary drug usage evaluation comparing rates of recurrent DVT/PE and major bleeding between dalteparin and enoxaparin supported the feasibility of the therapeutic interchange program, but no outcome data are available. Another institution replaced enoxaparin with dalteparin in 1996 as the sole LMWH on the formulary for prophylaxis of DVT/PE following orthopedic and abdominal surgery. Rates of recurrent DVT/PE and major bleeding seen with dalteparin were comparable to those that would have been expected with enoxaparin.
- A total of 8298 LMWH prescriptions were filled at MTFs in FY 2000. Approximately 96% of these were for enoxaparin.
- *Input from MTF providers* – Because of the morbidity and mortality associated with DVT and PE, the PEC sent its clinical review of LMWHs and a survey requesting input regarding the therapeutic interchangeability of the LMWHs to 30 providers in Internal Medicine, Cardiology, Hematology/Oncology, Ob/Gyn, Emergency Medicine, Orthopedics, and Family Practice. A total of 12 surveys (40%) were returned. Three other physicians also provided comments. Survey results are summarized in the following table:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
There are at least 2 LMWH products they would feel comfortable prescribing for DVT prevention/ treatment.	0	8	0	3	1
Providers would accept a contract for dalteparin for DVT prevention/treatment.	1	4	2	3	2
Providers would accept a contract for tinzaparin for DVT prevention/treatment.	0	4	1	5	2
Enoxaparin is used more because of familiarity than superiority.	1	4	0	5	0
Dalteparin is equal to enoxaparin for VTE treatment despite the lack of FDA approval.	0	6	0	3	2
Respondents would be more likely to be sued if a bad outcome occurred after prescribing dalteparin.	3	4	2	2	0

Given the morbidity and mortality associated with DVT/PE, the Council requires a high degree of certainty about the interchangeability of the drugs for these indications. The Council found insufficient data to confidently conclude that enoxaparin and dalteparin are equally efficacious for the outpatient treatment and prophylaxis of DVT. Although the survey of MTF providers revealed some support for a closed class contract, the responses showed insufficient support to pursue such a contract. The Council concluded that enoxaparin and dalteparin are not sufficiently interchangeable for a closed class contract for the outpatient treatment and prophylaxis of DVT.

G. *Role of the DoD P&T Executive Council in BPA development* –MAJ Cheryl Filby reported the recommendations of the subcommittee regarding the role of the DoD P&T Executive Council in the BPA development process. The Council voted to accept the subcommittee's recommendations:

- DSCP will coordinate all proposed DoD and DoD/VA blanket purchase agreements with the DoD P&T Executive Council (or the PEC acting on behalf of the Council) to ascertain whether the terms and conditions are in accord with the Council's strategy for managing the pertinent drug class. The DoD P&T Executive Council will accept or reject the terms of the agreement.
- If the P&T Executive Council accepts the agreement, DSCP will then be responsible for the content of the agreement in regard to legal and contractual sufficiency.
- Individual MTFs and TRICARE regions may continue to negotiate facility-specific incentive agreements. However, MTFs and TRICARE regions are encouraged to forward any agreements to DSCP for a review of legal sufficiency.

H. *Levofloxacin BPA* – At the Feb 01 meeting the Council asked DSCP to eliminate unacceptable provisions from the levofloxacin (Levaquin) BPA. The Council reviewed a revised BPA for levofloxacin and found that the unacceptable provisions had been eliminated. The BPA offers levofloxacin 250 mg and 500 mg to all MTFs for $2.00 per tablet. Continuation of the $2.00 price is contingent upon levofloxacin achieving either (1) an 80% aggregate DoD market share by 1 Aug 01, or (2) a 50% market share at individual MTFs. Market share will be based on patient days of therapy calculated from

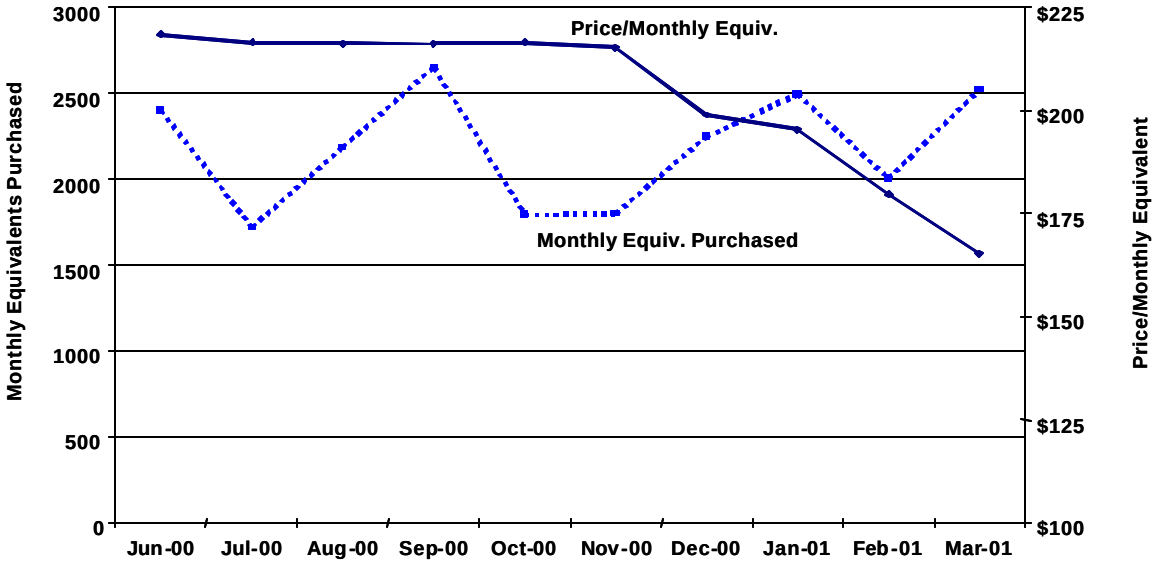
Uniformed Services Prescription Database (USPD) data. Levofloxacin is the only fluoroquinolone on the BCF, but the drug class remains "open," so MTFs may have additional fluoroquinolones on their formularies. As of April 2001, the aggregate market share for levofloxacin was approximately 77%.

I. *Status of BPAs for leutinizing hormone releasing hormone (LHRH) agonists* – A BPA makes goserelin (Zoladex) available to MTFs at the VA national contract price in exchange for attainment of an 80% overall share of the MTF prescriptions for LHRH agonists for prostate cancer by 1 Sep 2001.

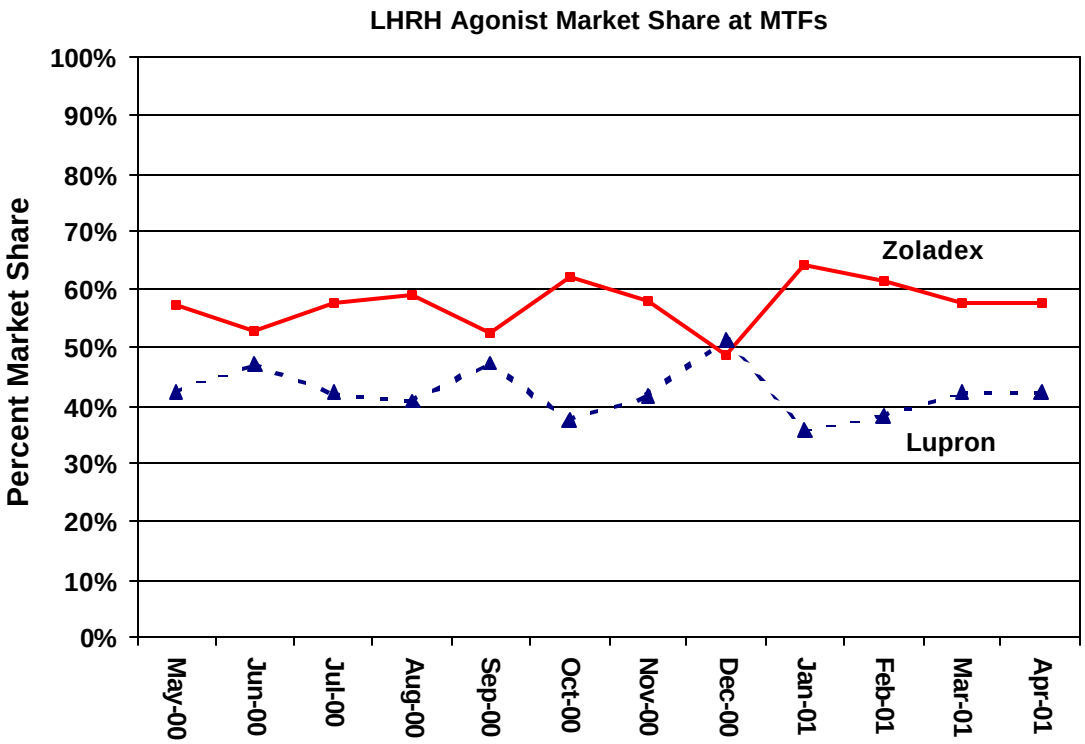
A BPA from TAP Pharmaceuticals makes leuprolide (Lupron) 1, 3, and 4-month depots available at a cost per dose just slightly higher than Zoladex. TAP modified the BPA in May 2001 so that the BPA price is available without any market share requirements (the original BPA required that Lupron attain an 80% market share within 6 months).

The Zoladex and Lupron BPAs have reduced the weighted average cost per monthly equivalent of LHRH agonist therapy for prostate cancer by 23% from $215 in Nov 00 to $165 in Mar 01. The BPAs yielded $294,000 in cost avoidance for MTFs from Nov 00 to Mar 01.

LHRH Agonist Price per Monthly Equivalent and Purchases at MTFs



Market share trends suggest that the 80% market share goal for Zoladex will probably not be achieved (see graph below). The Council asked DSCP and the PEC to talk with Astra Zeneca about the potential extension of the BPA price beyond August 2001 even if the 80% market share goal is not achieved.



The VA contract for Zoladex expires in February 2002. The Council asked the PEC to assess the potential for a contracting action for LHRH agonists for prostate cancer and present a recommendation at the August 2001 P&T Executive Council meeting.

J. *Proposed BPA for metformin/glyburide (Glucovance; BMS) and glyburide extended release (Glucophage XR; BMS)* – Bristol Myers Squibb (BMS) proposed a BPA that would reduce the price of Glucovance and Glucophage XR if they were added to the Basic Core Formulary. BMS also promised to further reduce the price of Glucovance and Glucophage XR to meet or beat any price offered on generic metformin until which point the generic metformin price falls below a price at which BMS can no longer compete. The proposed BPA did not specify the price at which BMS can no longer compete.

The Council concluded that there is insufficient evidence to prove conclusively that the extended release and combination dosage forms offer a clinically significant advantage regarding safety, tolerability, or efficacy over immediate release metformin or immediate release metformin plus generically available glyburide. While the proposed BPA would provide an economic benefit to DoD in the short run, it might be costly in the long run. DoD would benefit economically from the BPA until generic versions of metformin become available at a price below the BMS price protection point. If and when the price of generic metformin falls below the BMS price protection point, DoD would forgo the savings that could have been accrued through the use of the lower priced generic metformin because patients taking Glucovance or Glucophage XR would not likely switch back to generic metformin.

The current market share for various metformin products in MTF pharmacies, retail network pharmacies, and the NMOP are shown in the following table:

Number and percent of patient obtaining Rxs for various metformin products	MTFs	MCSC retail network	NMOP
Metformin (Glucophage)	42,756 (94%)	9,917 (72%)	4,912 (78%)
Extended release metformin (Glucophage XR)	2,401 (5%)	1872 (14%)	673 (11%)
Metformin/glyburide (Glucovance)	389 (1%)	1925 (14%)	722 (11%)
Totals	45,546	13,714	6,307

Note: time period is 4/1/01 through 5/25/01; data from the Pharmacy Data Transaction Service Customer Service Support Center

Since 94% of MTF patients using metformin products are currently using immediate release metformin (Glucophage), DoD has the potential to realize significant cost savings if these patients are treated with inexpensive generic versions of metformin in the future. The Council advised DSCP to reject the proposed BPA. The Council's rejection of the proposed BPA does not preclude an MTF from adding Glucovance or Glucophage XR to its formulary. MTFs should consider the local usage patterns and the degree to which their patients are getting prescriptions for Glucovance or Glucophage XR filled in retail pharmacies where the cost to DoD is much higher.

7. BCF ISSUES

A. *Proposal to add lancets to the BCF* – The Council decided not to add lancets to the BCF.

- Some MTFs provide lancets through central supply or other places in the MTF besides the pharmacy. There is no compelling reason to require all MTFs to provide lancets through the pharmacy.
- Standardization of medical and surgical supplies is being worked on a regional basis. Lancets and other items related to diabetic care might be more appropriately handled on a regional basis.

B. *Status of digoxin on the BCF* – The BCF listing for digoxin oral currently specifies Lanoxin brand (Glaxo Wellcome) only. The Council removed the specific brand designation from the listing because there is now an "A-rated" generic equivalent (Digitek; Bertek).

C. *Clarification of BCF listing for doxycycline oral* – Periostat (CollaGenex Pharmaceuticals) is a 20-mg capsule formulation of doxycycline hyclate with FDA approval as an adjunct to scaling and root planning to promote attachment level gain and pocket depth in patients with adult periodontitis. The mechanism of action is not antimicrobial, but is related to doxycycline's ability to inhibit collagenase.

The Council excluded Periostat from the BCF listing for doxycycline oral due to its low usage across the system (503 bottles of 100 purchased in the last 12 months, 65% of these by two large medical centers), its high cost relative to generic doxycycline, and the absence of a compelling reason to require all MTFs to have it on their formularies.

D. *Clarification of methylphenidate listing on the BCF* – The Council excluded Metadate CD from the BCF listing for methylphenidate oral.

- Metadate CD offers no safety or tolerability advantage compared to other dosage forms of methylphenidate already on the BCF.

- Metadate CD has an 8-hour duration of action. Concerta has a 12-hour duration of action and is on the BCF. With a shorter duration of action, Metadate CD is less likely than Concerta to eliminate the need for repetitive dosing.
- An FSS price is not yet available for Metadate CD and actual dose distributions for Metadate CD and Concerta are unknown, so a precise cost comparison is impossible. Assuming "standard" FSS pricing and a dosage distribution similar to that seen in clinical trials, the estimated weighted average daily cost of Metadate CD is $1.27. Concerta would be only slightly more expensive. The estimated weighted average daily cost for Concerta (based on manufacturer-supplied daily consumption data) is $1.42, $1.52 and $1.70 for the 54 mg, 36 mg and 18 mg strengths respectively.
- Metadate CD is a controlled substance, so all MTFs would experience the administrative burden associated with accounting for an additional controlled drug if Metadate CD were added to the BCF.
- The Council does not want to add another dosage form of methylphenidate to the BCF until it assesses how well Concerta reduces the frequency of midday dosing.

E. *Status of nifedipine extended release on the BCF* – The BCF listing for nifedipine extended release currently specifies Adalat CC as the BCF selection. At the last meeting, the DoD P&T committee requested that the PEC report back on whether the availability and pricing of generic nifedipine extended release products necessitated a change in the BCF listing. After reviewing the current availability and prices for generic versions of both Procardia XL and Adalat CC, the Council concluded that it is not necessary to make changes in the Basic Core Formulary until a generic manufacturer offers prices that are competitive with Adalat CC. The PEC will continue to monitor pricing for nifedipine extended release products.

8. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove micronized glyburide from the BCF* – Glyburide oral and micronized glyburide are both listed on the BCF. An Air Force pharmacist requested that micronized glyburide be removed from the BCF because it is seldom used and more costly than other glyburide formulations. Alternately, he requested that a DoD or VA/DoD contracting initiative be considered to reduce the unit cost of the drug.

The safety, tolerability, and efficacy of glyburide and micronized glyburide appear to be similar. The primary difference between the formulations is improved and more consistent bioavailability with the micronized product, resulting in a less variable half-life and a lower propensity for food to interfere with absorption. The duration of action is similar with both drugs (16-24 hours), due to intracellular accumulation of glyburide. It is unclear whether the pharmacokinetic differences result in any improvement in glycemic control.

Generic micronized glyburide is at least 2 to 3 times more costly than generic glyburide. Of the 15.2 million sulfonylurea tablets or capsules purchased by MTFs through the Prime Vendor program during the first quarter of FY 01, 44% were glyburide; 43% glipizide, 10% micronized glyburide, 2% glimepiride, and essentially 0% tolazamide, tolbutamide, or chlorpropamide. A joint VA/DoD contracting initiative that includes micronized glyburide is already in progress.

The Council did not make any changes to the BCF pending results of the contracting initiative for micronized glyburide.

B. *Request to add gatifloxacin (Tequin) and remove levofloxacin (Levaquin) from the BCF* – A Director of Pharmacy Services at an Air Force MTF cited a price advantage for gatifloxacin in a request to replace levofloxacin with gatifloxacin on the BCF. Gatifloxacin is available to MTFs through an incentive price agreement at a price of $1.90 for the 200 mg and 400 mg tablets. The incentive price is contingent on gatifloxacin having a preferred or co-preferred formulary position at an individual MTF, but there are no market share requirements.

   The Council voted to keep levofloxacin on the BCF. Removal of levofloxacin from the BCF would nullify the BPA that makes levofloxacin available to all MTFs at a price of $2.00 per dose. MTFs are reminded that the fluoroquinolone class is open on the BCF, so MTFs may add gatifloxacin to their formularies if they wish to take advantage of the lower price for gatifloxacin.

C. *Requests to add tolterodine extended release capsules (Detrol LA) to the BCF* – MAJ Roach reported that the PEC received 10 requests for addition of Detrol LA to the BCF in a single week. With the exception of one request from an obstetrician-gynecologist, the requests came from specialty providers (urogynecology or urology). Four requestors noted that tolterodine extended release should be considered a second line agent after the patient has failed oxybutynin; two of the four specifically mentioned tolerability and compliance benefits in elderly patients who could not tolerate oxybutynin. Three requestors cited comparable costs for the tolterodine immediate release and extended release preparations. One requestor felt that tolterodine had become standard of care in community and academic practice for treatment of Overactive Bladder (OAB). The Council considered these requests as part of the overall review of OAB drugs (see Paragraph 9C).

D. *Review of form for requesting BCF changes on PEC website* – MAJ Roach reported that requestors provided little information about how the requested drug compared to other drugs regarding safety, tolerability, efficacy and price. The Council agreed with the PEC recommendation to change the wording on the form to more clearly ask MTF providers to compare the requested agents to other drugs on the BCF or in the same drug class.

9. BASIC CORE FORMULARY REVIEW

A. *Ongoing review* – The PEC is reviewing topical medications for acne and benzodiazepines for anxiety disorders. Information on these drugs will be presented at the next meeting of the P&T Executive Council.

B. *Review of topical corticosteroids for the BCF* – MAJ Barbara Roach reported on the PEC review of topical corticosteroids (see Appendix D for a table of topical corticosteroid agents). Topical corticosteroids were grouped by potency category, ranging from Class I (Very High Potency Agents) to Class IV (Low Potency Agents). According to input from dermatologists, primary care providers, and others, there is little or no difference within potency categories except for the difference between fluorinated and nonfluorinated agents and availability in the desired vehicle (e.g., ointment, cream). The Council considered each potency category for potential changes to the BCF:

Class I Agents (Very High Potency) – There is currently no Class I agent on the BCF. These agents are not generally considered to be primary care drugs. No agent from this class was added to the BCF.

Class II Agents (High Potency) – There are currently no Class II agents on the BCF. After considering the opinions of dermatologists and primary care providers and the relative usage and cost per gram for specific agents within this category, the Council decided to add fluocinonide 0.05% cream to the BCF.

Fluocinonide represents 58% of all MTF purchases of Class II agents (by number of tubes) and is available under a VA/DoD national contract at approximately $0.10 per gram. (Costs per gram in this category range as high as $1.17 per gram). Fluocinonide 0.05% cream represents the great majority of all purchases of fluocinonide products. MTFs may decide whether or not to add fluocinonide 0.05% ointment or solution to their formularies according to local usage patterns.

Class III Agents (Medium Potency) – Triamcinolone 0.1% is currently listed on the BCF as "triamcinolone acetonide 0.1% topical." The Council did not add another Class III agent to the BCF.

The Council agreed that listings for topical agents on the BCF should specify formulation (e.g., cream, ointment) and concentration. After considering the relative usage of the various formulations, the Council clarified the listing to "triamcinolone acetonide 0.1% cream." To avoid confusion, the Council instructed the PEC to clarify the definitions section on the BCF page of the PEC website to note that formulary requirements for topical agents include only the specified formulation(s) and strength(s). The PEC will review the BCF to see if further clarifications are necessary for individual topical agents.

Class IV Agents (Low Potency) – The only low potency topical corticosteroid on the BCF is hydrocortisone 2.5% rectal cream. The Council discussed addition of a Class IV nonfluorinated topical corticosteroid agent for general use. Nonfluorinated agents cause less skin atrophy than fluorinated agents, which is particularly important for pediatric patients and for administration to the face.

The majority of MTFs already have hydrocortisone cream on their individual formularies and many also have desonide (both are nonfluorinated). Hydrocortisone cream and ointment are available in both OTC and prescription formulations. The BCF generally does not include OTC medications, so the Council did not add hydrocortisone cream or ointment to the BCF. The Council also did not add desonide to the BCF because it costs approximately eight times more per gram than hydrocortisone, and the Council did not wish to mandate that facilities using hydrocortisone cream must also add desonide to their formularies.

C. *Review of medications for overactive bladder (OAB) for the BCF* – Oxybutynin immediate release is the only medication for overactive bladder currently on the BCF. Tolterodine (Detrol, Detrol LA) and oxybutynin extended release (Ditropan XL) have a lower incidence of anticholinergic side effects (e.g. dry mouth) than oxybutynin immediate release. The clinical significance of the lower incidence of side effects is uncertain because the percentage of patients who discontinued these drugs due to side effects in clinical trials is small and not clinically or statistically different between the

drugs. Ditropan XL, Detrol, and Detrol LA all cost more than 10 times as much as oxybutynin immediate release. The Council concluded that Ditropan XL, Detrol, and Detrol LA should not be added to the BCF because they do not offer sufficient clinical benefit to justify their significantly higher cost compared to oxybutynin immediate release.

D. *Review of sedative/hypnotic medications for the BCF* – Temazepam and zolpidem currently account for over 90% of sedative/hypnotic medications dispensed from MTF pharmacies. One or more of these drugs are present on 90% of MTF formularies, and 55% of MTFs have both drugs on formulary. The Council considered only these two sedative/hypnotic medications for addition to the BCF.

   Eighty percent of MTFs have temazepam on formulary, but prime vendor data show that usage is declining. Council members speculated that usage is shifting toward newer agents that might have a lower propensity to cause tolerance and dependence in long term use). The Council concluded that temazepam should not be added to the BCF because there is no clinical reason to require 20% of the MTFs to add it to their formularies.

   Sixty-five percent of MTFs have zolpidem on formulary. Anecdotal reports suggest continued efficacy of zolpidem in long-term use without the development of tolerance or dependence; however, clinical trial evidence is limited to trials of 35 days or less. Zolpidem costs more than 40 times as much as temazepam. The Council concluded that zolpidem should not be added to the BCF because the magnitude of the incremental clinical benefit is uncertain and the incremental cost is too large to require every MTF to have it on their formularies.

   No changes were made to the BCF. The sedative/hypnotic class will not be represented on the BCF at this time.

10. The meeting adjourned at 0900 hours on 7 June 2001. The next meeting will be held at Ft Sam Houston, TX and is scheduled for 15 Aug 01 at 0800. All agenda items should be submitted to the co-chairs no later than 20 Jul 01.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

LIST OF APPENDICES

Appendix A: MTF Expenditures for Drugs Included in the Advances in Medical Practice (AMP) Program

MTF Expenditures on AMP Drugs, First Six Months of FY 01

Drug Name*	Air Force	Army	Navy	Grand Total
Abciximab	$153,356	$135,960	$61,384	$350,699
Alpha-1-Proteinase Inhibitor			$5,676	$5,676
Becaplermin	$42,589	$55,966	$28,194	$126,749
Cyclosporine	$229,898	$157,445	$119,904	$507,247
Cyclosporine Microemulsion	$465,749	$425,208	$436,010	$1,326,967
Dornase Alfa	$160,855	$92,255	$112,092	$365,203
Epoetin Alfa	$2,083,361	$2,444,833	$1,197,215	$5,725,408
Eptifibatide	$38,665	$198,383	$124,977	$362,025
Etanercept	$804,539	$529,045	$300,484	$1,634,069
Factor VIIa,Recomb				
Filgrastim	$713,677	$880,520	$499,944	$2,094,141
Gemcitabine Hcl	$107,075	$205,731	$123,202	$436,008
Glatiramer Acetate	$258,059	$116,704	$64,836	$439,600
Infliximab	$153,880	$153,784	$187,743	$495,407
Interferon Beta-1a	$851,257	$632,273	$322,213	$1,805,742
Interferon Beta-1b	$280,715	$361,135	$237,275	$879,125
Interferon Gamma-1b,Recomb.	$30,794	$25,793	$20,854	$77,441
Irinotecan Hcl	$114,396	$303,743	$126,862	$545,001
Leflunomide	$105,700	$189,325	$103,047	$398,072
Mycophenolate Mofetil	$282,012	$333,083	$151,995	$767,090
Mycophenolate Mofetil HCl	$460	$1,681		$2,141
Palivizumab	$1,261,189	$1,294,001	$851,639	$3,406,830
Ribavirin/Interferon A-2b	$398,410	$899,484	$297,228	$1,595,122
Rituximab	$143,969	$660,609	$203,242	$1,007,820
Sargramostim	$14,918	$75,739	$7,850	$98,507
Sirolimus	$20,452	$43,216	$22,488	$86,155
Tacrolimus Anhydrous	$293,731	$241,897	$167,910	$703,538
Temozolomide	$83,072	$72,879	$51,571	$207,522
Tirofib Hc M-Hyd/Na Chlor 0.9%	$2,023	$21,087		$23,109
Tirofiban HCl M-Hydrate	$62,628	$47,964	$15,166	$125,759
Trastuzumab	$69,227	$153,578	$10,647	$233,452
Grand Total	**$9,226,657**	**$10,753,321**	**$5,851,648**	**$25,831,626**

* Celecoxib and rofecoxib were removed from the AMP list for FY 01

Appendix B: Implementation Guidance for the Non-Sedating Antihistamine Contract

Note: The following implementation plan was distributed to the field via e-mail the last week of April 2001.

Implementation Plan for the Non-Sedating Antihistamine Contract

Department of Defense Pharmacoeconomic Center

Effective Date: 1 May 2001 (Contract will be in effect for one year with an option to extend the terms of the contract for 4 additional one-year periods).

Selected Product: Fexofenadine (Allegra®) 60 mg tablets and 180 mg tablets; Aventis Pharmaceuticals Inc.

Contract Prices

Table 1

Strength	Dosage Form	NDC	Price per tablet/capsule	QTY per Package
60 mg	Tablet	00088-1107-47	$0.37	100
60 mg	Capsule*	00088-1102-55	$0.37	500
180 mg	Tablet	00088-1109-47	$0.60	100

* Aventis Pharmaceuticals informed the Pharmacoeconomic Center that production of the Allegra® 60mg capsule product will be phased out over the next 12 months. The contract price of $0.37 for the 60mg capsule only applies to the 500-count package size. The contract price for the 60mg capsule will only apply until such time that the 500-count package size of the Allegra 60mg tablet is available. We suggest that MTFs **not** add the 60 mg capsule to their formularies, as it will necessitate switching patients to the tablet formulation in the near future.

Formulary guidance

- This contract closes the non-sedating antihistamine (NSA) class on the Basic Core Formulary (BCF) and therefore:
  1) Allegra® 60 mg tablets and Allegra® 180 mg tablets must be on all Military Treatment Facility (MTF) formularies.
  2) Claritin® 10 mg tablets and Claritin Reditabs® must not be on any MTF formularies.
- Table 2 delineates formulary status requirements for all Allegra® and Claritin® products. While MTFs are not precluded from having the products in column 3 on formulary, MTFs should only include these products on formulary if the needs of their specific patient population require their availability. This decision requires critical evaluation of the relative costs of all products that can meet the clinical needs of patients.

Table 2

MTFs must have on formulary:	MTFs cannot have on formulary:	MTFs may have on formulary:
Allegra 180 mg tablets	Claritin Reditabs	Allegra 60 mg capsules
Allegra 60 mg tablets	Claritin 10 mg tablets	Allegra 30 mg tablets
		Allegra D
		Claritin Syrup
		Claritin D 12 Hour
		Claritin D 24 Hour

- Other NSAs that may be approved by the FDA after the date of this announcement may not be added to MTF formularies during the term of this contract.
- Cetirizine (Zyrtec®) is classified as a second-generation antihistamine but is not classified as an NSA. Therefore, this contract does not affect the current or future BCF or MTF formulary status of Zyrtec® products.
- This contract does **not** affect the current or future status of any Allegra®, Claritin®, or Zyrtec® product on the National Mail Order Pharmacy (NMOP) formulary. All Allegra®, Claritin® and Zyrtec® products remain available through the NMOP. Please note that the contract price for the Allegra® products as presented in Table 1 *will* apply to the NMOP.
- This contract does **not** apply to Managed Care Support Contractor retail network pharmacies.

Prescribing guidance for prescriptions filled at MTFs

- **New patient starts (patients who have not previously been prescribed a Claritin â or Allegra â product):** The contract requires that all new patients who have a clinical need for an NSA be prescribed either Allegra® 60 mg tablets or Allegra®180 mg tablets. If the patient fails to achieve adequate symptom relief or experiences unacceptable side effects with Allegra®, it is permissible to prescribe Claritin® under the provisions of medical necessity. Other examples of medical necessity include:
  - documented allergy to Allegra® products
  - pregnant patients with a clinical need for an NSA (Claritin® is assigned a pregnancy risk category B. Allegra® is assigned a pregnancy risk category C)
- **Patient who were previously treated successfully with Claritin 10mg or Claritin Reditabs:** Unlike the contracts currently in place for the proton pump inhibitor and statin drug classes, this contract does not mandate the conversion of NSA patients currently receiving Claritin® 10 mg tablets or Claritin Reditabs® to Allegra® 60 mg tablets or Allegra® 180 mg tablets. It is therefore **permissible** for patients who were successfully treated with Claritin® 10 mg tablets or Claritin Reditabs® to continue to receive these products. However, it is important to note that while the contract does not mandate patients be switched, **MTFs may decide to encourage their providers to switch patients.** This decision will be made at the MTF level.
- This contract does not preclude providers from prescribing alternate agents to patients for whom the contracted dosage forms and strengths are clinic ally inappropriate (i.e., pediatric patients).
- Both Allegra® 180 mg tablets and Allegra® 60 mg tablets are included in the NSA contract. This gives providers greater flexibility by allowing them to prescribe either Allegra® 60 mg in the morning and a generic sedating antihistamine in the evening at a cost of approximately $0.40 per day, Allegra® 180 mg once daily at a cost of $0.60 per day, or Allegra® 60 mg twice daily at a cost of $0.74 per day.

Points of Contact:

Note: Points of contact changed from initial version due to personnel changes at the Pharmacoeconomic Center

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Appendix C: Cost Avoidance in DoD MTFs Due to National Pharmaceutical Contracts, First 6 months of FY01 (Oct 00 – Mar 01)

Estimated Cost Avoidance in DoD MTFs Due to National Pharmaceutical Contracts, First Six Months of Fiscal Year 2001						
Drug/Drug Class	**Contract Start Date**	**Weighted Average Price/Unit Before Contract**	**Theoretical 1st and 2nd Quarter FY 01 Cost If Not Contracted**	**1st and 2nd Quarter FY 01 Actual Cost**	**Cost Avoidance**	**Percent Reduction in Cost**
Statins	1-Oct-99	$0.961874	$40,684,953	$31,484,021	$14,510,274	35.66%
PPIs	1-Oct-99	$1.681407	$50,953,184	$34,252,261	$16,700,923	32.78%
Lisinopril	1-Aug-99	$0.284396	$11,378,013	$6,869,586	$4,508,426	39.62%
Diltiazem	15-Dec-98	$0.631469	$6,373,438	$3,493,867	$2,879,571	45.18%
Ranitidine	16-Nov-98	$0.066602	$1,841,140	$1,544,368	$296,772	16.12%
Hepatitis A	18-Sep-99	$16.981597	$4,452,914	$2,967,127	$1,485,788	33.37%
Albuterol	16-Nov-98	$3.297032	$1,437,275	$1,749,002	($311,727)	-21.69%
Timolol Gel	14-Jan-00	$14.598153	$625,487	$255,067	$370,420	59.22%
Verapamil	20-Aug-99	$0.125912	$1,188,225	$821,203	$367,022	30.89%
Cimetidine	16-Nov-98	$0.072763	$332,088	$187,941	$144,147	43.41%
Terazosin	5-Sep-00	$0.459093	$4,014,631	$1,991,315	$2,023,316	50.40%
Captopril	18-Oct-99	$0.036173	$97,191	$56,579	$40,612	41.79%
Nortriptyline	15-Oct-99	$0.049281	$151,200	$111,120	$40,079	26.51%
Gemfibrozil	1-Jan-00	$0.077935	$530,685	$536,119	($5,433)	-1.02%
Naproxen	3-Jul-00	$0.069829	$1,384,510	$1,363,885	$20,625	1.49%
Amoxicillin	7-Aug-99	$0.040549	$291,247	$286,829	$4,417	1.52%
Insulin Syringes	1-May-00	$0.098121	$577,609	$407,346	$170,263	29.48%
Timolol Drops	14-Jan-00	$2.795264	$115,908	$94,615	$21,294	18.37%
Nicotine Patches	1-Jun-00	$2.567746	$751,541	$638,886	$112,654	14.99%
Levobunolol	14-Jan-00	$4.641527	$30,356	$21,778	$8,578	28.26%
Fluocinonide	1-Sep-99	Cream $1.816402 Oint $6.210282 Sol $6.422653	$179,959	$178,805	$1,154	0.64%
Prazosin	1-Nov-99	$0.032916	$63,057	$55,562	$7,495	11.89%
Amantadine	28-Aug-99	$0.063871	$31,744	$28,649	$3,095	9.75%
Naproxen Sodium	3-Jul-00	$0.073176	$78,586	$74,645	$3,941	5.01%
Salsalate	15-Mar-00	$0.026462	$59,335	$74,599	($15,264)	-25.73%
Insulin	1-Nov-99	$5.292812	$2,593,605	$2,726,349	($132,744)	-5.12%
Acyclovir	1-Oct-00	$0.121623	$462,557	$414,140	$48,416	10.47%
Azathioprine	1-Oct-00	$0.477152	$389,785	$349,282	$40,503	10.39%
Hydroxyurea	1-Oct-00	$0.295324	$78,497	$79,258	($761)	-0.97%
Pentoxifylline	1-Oct-00	$0.182262	$385,192	$383,409	$1,782	0.46%
Rifampin	1-Oct-00	$0.566776	$93,201	$86,415	$6,786	7.28%
Sucralfate	1-Oct-00	$0.198476	$192,692	$192,541	$152	0.08%
Acetaminophen	1-Jan-01		NA	NA	NA	NA
TOTAL			**$131,819,804**	**$93,776,570**	**$43,352,575**	**32.89%**

Explanation of Cost Avoidance Calculations: Cost avoidance equals the difference between (1) the theoretical cost that would have occurred in FY 00 if a contract had not existed, and (2) the actual cost that was incurred in FY 01 for the "market basket" of drugs that pertains to each contract. The theoretical cost that would have occurred in FY 01 if a contract had not existed was estimated by multiplying the weighted average price/unit that existed before the contract took effect by the quantity purchased in FY 01. The "market basket" of drugs includes both the contracted and the non-contracted drugs that pertain to a given contract. For example, the cost avoidance for statins takes into account the expenditures for all six statins, not just the two contracted statins.

Appendix D –Topical Corticosteroid Table

After receiving input from dermatology consultants, providers, and pharmacists, topical corticosteroids were divided into four categories depending on potency. The potency of a topical corticosteroid is standardized according to its ability to induce vasoconstriction. This is partially determined by the concentration of the drug and the vehicle used. The categories range from Class I (Very High Potency Agents) to Class IV (Low Potency Agents).

Ranking the topical corticosteroids in this manner may present some discordance among different classification schemes when attempting to categorize a specific drug into a particular level of potency; overall, however, disagreements are minor. Disease severity, age, body location and concomitant medical conditions usually determine the potency of topical corticosteroid treatment, while characteristics of the dermatologic condition usually determine the vehicle chosen. There appears to be little clinical reason to prefer one drug to another within a given category except for availability in the desired vehicle and a preference for nonfluorinated products for pediatric use or use on the face. Nonfluorinated products appear to cause less skin thinning (atrophy).

Topical Corticosteroids Categorized by Potency

Class I – Very High Potency			
Brand Name	**Generic Name**	**Vehicle**	**(%)***
Diprolene	Augmented betamethasone dipropionate □	Ointment	0.05
Temovate, Cormax, Temovate E	Clobetasol propionate □	Cream, Ointment, Gel, Solution	0.05
Psorcon	Diflorasone diacetate □	Ointment	0.05
Ultravate	Halobetasol propionate □	Cream, Ointment	0.05

Class II – High potency			
Brand Name	**Generic Name**	**Vehicle**	**(%)***
Cyclocort	Amcinonide □ □	Cream, Ointment, Lotion	0.1
Diprolene AF	Augmented betamethasone dipropionate □ □	Cream	0.05
Alphatrex, Del-Beta, Diprosone, Maxivate	Betamethasone dipropionate □ □	Cream, Ointment, Lotion	0.05
Betatrex	Betamethasone valerate □ □	Ointment	0.1
Topicort	Desoximetasone □	Cream, Ointment Gel	0.25 0.05
Florone, Florene-E emollient, Maxiflor	Diflorasone diacetate □	Cream, Ointment (emollient base)	0.05
Synalar-HP	Fluocinolone acetonide □	Cream	0.2
Lidex, Lidex-E, Lidex soln.	Fluocinonide □	Cream, Ointment, Solution, Gel	0.05
Halog (water soln cream), Halog solution, Halog-E	Halcinonide □	Cream, Ointment, Solution	0.1
Aristocort, Aristocort A Kenalog, Trymex	Triamcinolone acetonide □ □	Cream, Ointment	0.5

Topical Corticosteroids Categorized by Potency (continued)

Class III – Medium potency			
Brand Name	**Generic Name**	**Vehicle**	**(%)***
Benisone, Uticort	Betamethasone benzoate □	Cream, Gel, Lotion	0.025
Alphatrex, Diprosone	Betamethasone dipropionate □	Lotion	0.05
Valisone, Beta-Val, Betatrex	Betamethasone valerate □	Cream, Lotion	0.1
Cloderm	Clocortolone pivalate □	Cream	0.1
Topicort LP	Desoximetasone □	Cream, Gel	0.05
Fluonide, Synalar, Synemol	Fluocinolone acetonide □	Cream, Ointment	0.025
Cordran	Fluandrenolide □	Cream, Ointment Lotion	0.025, 0.05 0.05
Cutivate	Fluticasone propionate □	Cream Ointment	0.05 0.005
Locoid	Hydrocortisone butyrate □	Cream, Ointment, Solution	0.1
Westcort	Hydrocortisone valerate □	Cream, Ointment	0.2
Elocon	Mometasone furoate □ □	Cream, Ointment Lotion	0.1
Aristocort A, Kenalog, Trymex,	Triamcinolone acetonide □ □	Cream, Ointment Lotion	0.025 0.025, 0.1

Class IV – Low potency			
Brand Name	**Generic Name**	**Vehicle**	**(%)***
Aclovate	Alclometasone dipropionate □	Cream, Ointment	0.05
Valisone, Celestone	Betamethasone valerate □	Cream	0.01, 0.2
DesOwen, Tridesilon	Desonide □	Cream, Ointment, Lotion	0.05
Decaderm	Dexamethasone □	Gel	0.1
Synalar, Fluonid	Fluocinolone acetonide □	Cream, Solution	0.01
Hytone, Lacticare, Synacort	Hydrocortisone □	Lotion Cream, Oint, Lotion Cream, Oint, Lotion, Solution Cream, Oint, Lotion	0.25 0.5 1 2.5
Numerous	Hydrocortisone acetate □	Cream, Ointment	0.5, 1
Medrol	Methylprednisolone □	Cream	0.25
Oxylone	Fluoromethalone □	Cream	0.025
Numerous OTCs			

□ fluorinated agent; □ nonfluorinated agent; □ disagreement among references concerning potency class
* Not all brands or concentrations are available in all vehicles or formulations; specialized formulations such as aerosols or tapes are not included in this table

Department of Defense
Pharmacoeconomic Center

1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE **8 FEB 2001**

MEMORANDUM FOR: Executive Director of Tricare Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0800 hours on 8 February 2001, at Ft Sam Houston, TX.

2. **MEMBERS PRESENT**:

CDR Terrance Egland, MC	Co-chair
COL Daniel D. Remund, MS	Co-chair
COL Mark Nadeau, MC	Air Force (alternate)
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Matt Nutaitis, MC	Navy
MAJ Brett Kelly, MS	Army
CDR Robert Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Health Net Federal Services
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest

MEMBERS ABSENT:

COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
CDR Kevin Cook, MSC	Navy
Ron McDonald	Sierra Military Health Services
Joint Readiness Clinical Advisory Board Representative	

OTHERS PRESENT:

CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
COL Mike Heath, MS	Army Pharmacy Consultant, DoD Pharmacy Board of Directors
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
COL William Davies, MS	DoD Pharmacy Program Director, Tricare Management Activity (TMA)
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC Ed Zastawny, BSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	Lead Agent Office, Region 9
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
CAPT Krissa Crawford, BSC	Pharmacy Practice Resident, Wilford Hall Medical Center
HM3 Cory Beckner	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
David Chicoine	Uniformed Services Family Health Plan
Eugene Moore	DoD Pharmacoeconomic Center
Mark Petruzzi	Merck-Medco
Elizabeth Scaturro	Merck-Medco
Carol Scott	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dana Dallas	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia

3. **ADMINISTRATIVE ISSUES**

   The minutes from the last meeting were accepted as written.

4. **REPORT FROM THE DOD EXECUTIVE COUNCIL MEETING** – COL Remund reported that the DoD P&T Executive Council added 12 drugs to the Basic Core Formulary (BCF) at the 7 Feb 01 meeting. Budget shortfalls in the Defense Health Program for FY 01 forced the Council to be very conservative in adding drugs to the BCF.

5. **IMPLEMENTATION OF FY 00 AND FY 01 NATIONAL DEFENSE AUTHORIZATION ACTS** – COL Davies briefed the Committee on the ongoing efforts to implement the pharmacy benefit provisions of the FY 00 and FY 01 National Defense Authorization Acts.

6. **BCF AND NATIONAL MAIL ORDER PHARMACY (NMOP) FORMULARY ISSUES** – The Committee determined the NMOP formulary status; NMOP or retail network formulary restrictions (NMOP Preferred Drug Program, quantity limits, or prior authorization); and the BCF status for six new drugs listed in Appendix A.

7. **NON-PREFERRED/PREFERRED DRUG PAIRS IN THE NMOP** – Eugene Moore (PEC) reported cost avoidance associated with the NMOP Preferred Drug Program (see Appendix B).

8. PRIOR AUTHORIZATIONS

A. *Cost avoidance from NMOP prior authorizations (PAs)* – Shana Trice (PEC) reported on the estimated cost avoidance due to NMOP prior authorizations. The cost avoidance per prescription is based on the cost avoidance model that was outlined in the Aug 00 DoD P&T Committee minutes.

PA Cost Avoidance per New Prescription Submitted to the NMOP

Drug	3rd Quarter FY 00	4th Quarter FY 00	1st Quarter FY 01
Sildenafil	$13.60	$26.46	Not calculated
COX-2 inhibitors	$11.66	$18.56	$10.95
Etanercept	$327.20	$111.86	$7.89

1) *Sildenafil* – Data reported by Merck Medco and DSCP suggest that a large number of the PAs performed during the first quarter FY 01 were for sildenafil refills. PA cost avoidance was not calculated for the first quarter of FY 01 because the cost avoidance model was not designed to account for prior authorization of refill prescriptions. The PEC will work with Merck Medco and DSCP to revise the model.

2) *Etanercept* – The large drop in the PA cost avoidance for etanercept is due to fewer prescription denials through the PA process (see following table).

NMOP PA Data for Etanercept

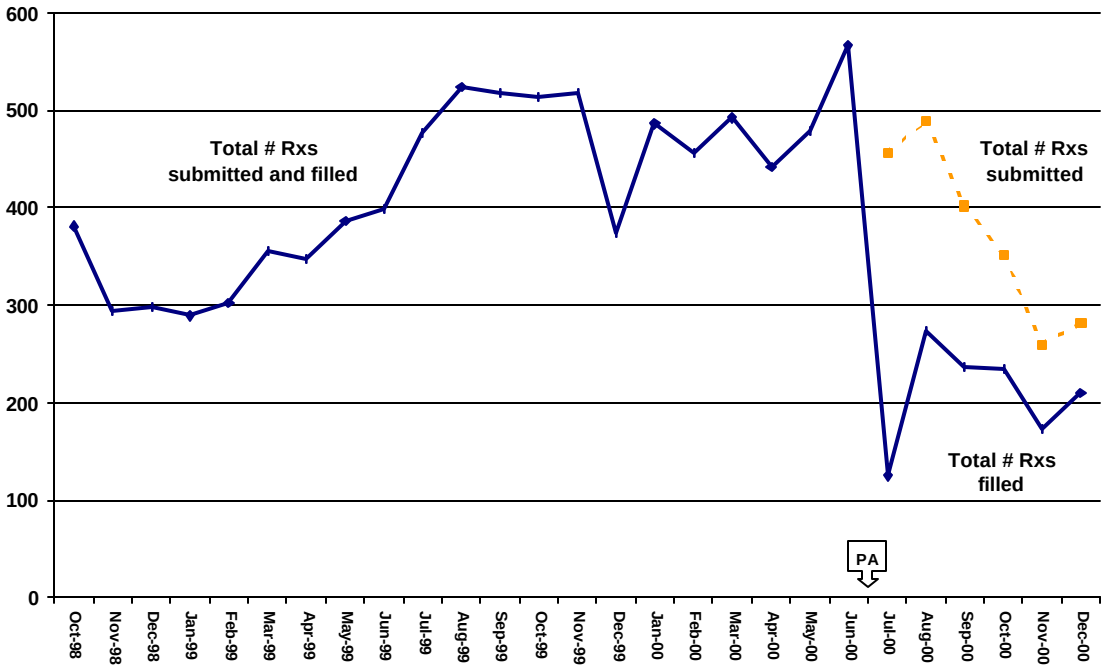
	3rd Quarter FY 00	4th Quarter FY 00	1st Quarter FY 01
Total number of Rxs filled (new and refill)	441	495	612
Total number of Rxs that went through the PA process	41	64	58
Total number of Rxs denied as a result of the PA process	11	5	1
Estimated cost avoidance per new Rx submitted	$327.20	$111.86	$7.89

The Committee discussed the possibility of modifying or discontinuing the PA for etanercept since the cost avoidance is so minimal. The Committee refrained from changing the etanercept PA because this analysis does not assess the PA cost avoidance in the retail pharmacy networks (which probably fill many more prescriptions for etanercept than the NMOP). The Committee encouraged the MCSC pharmacy directors to voluntarily provide data to the PEC for analysis of the etanercept PA cost avoidance in the retail networks (the MCSC pharmacy directors are not contractually required to submit the data). The PEC will furnish a list of data elements in the cost avoidance model to the MCSC pharmacy directors.

B. *Antifungals for onychomycosis* – The PA for onychomycosis began on 1 Jul 00 in the NMOP. Comparing the six-month time periods before and after the PA took effect, prescription fills for terbinafine and itraconazole dropped from an average of 491 per month (range 444-569) to an average of 211 per month (range 129-239). Prescription fills for terbinafine and itraconazole dropped because (1) prescriptions submitted to the NMOP were denied when they did not meet

the PA criteria, and (2) fewer prescriptions for terbinafine and itraconazole were submitted to the NMOP due to the "sentinel" effect of the PA. The sentinel effect occurs because providers prescribe the drug less frequently when they know the drug is subject to prior authorization. The following graph illustrates the reduction in the number of prescriptions submitted and the number of prescriptions filled for terbinafine and itraconazole after the PA began.

Total Number of NMOP Rxs for Terbinafine or Itraconazole



C. *Revision of PA forms* – Merck-Medco added clinical rationale language to the PA forms it faxes to prescribers for sildenafil and etanercept. The clinical rationale language is not yet in place on the Merck-Medco PA fax forms for COX-2 inhibitors or antifungals for onychomycosis.

D. *Changes to COX-2 inhibitor criteria to include Familial Adenomatous Polyposis (FAP)* – At the Aug 00 meeting, the Committee approved a change in the criteria for the COX-2 inhibitors to allow use of celecoxib for familial adenomatous polyposis. Merck-Medco has revised their fax form. The PEC will reflect the changes on its website.

E. *Proposal to change the COX-2 inhibitor PA to reflect findings of the Celecoxib Long-term Arthritis Safety Study (CLASS)* – The annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers were not significantly different for celecoxib versus NSAIDS for patients in the CLASS study who were also receiving low dose aspirin. The data, however, were limited: the number of patient-years of therapy for patients also receiving low dose aspirin was relatively low, results were based on a maximum of 6 months of therapy, and the dropout rates in both the celecoxib and NSAID group were high (40-45%).

The CLASS study suggests that the use of even low doses of aspirin may reduce or eliminate the GI protective effect of COX-2 selective NSAIDs compared to conventional NSAIDS. However, the Committee agreed that the data are insufficient to change the PA criteria to preclude usage of COX-2 inhibitors by patients taking low dose aspirin. The Committee requested that the PEC revise the clinical rationale language on the PA forms to include information on the results of the CLASS study in regard to the use of COX-2 inhibitors in patients currently receiving low dose aspirin.

F. *Prior authorization of ciclopirox topical solution (Penlac Nail Lacquer) in the NMOP and retail network* – LTC Ed Zastawny (PEC) reported on a request from one of the MCSCs to add ciclopirox topical solution to the existing PA for antifungals for onychomycosis. Since other drugs for onychomycosis require prior authorization to ensure that they are used only when clinically appropriate (when a fungal infection is present), the Committee agreed that the same standard should be applied to ciclopirox. The committee voted to institute a PA for ciclopirox topical solution that requires confirmation of a fungal infection.

9. **STATUS OF LOW MOLECULAR WEIGHT HEPARINS (LMWHs) IN THE NMOP AND RETAIL NETWORK**

The Committee discussed the potential need to have LMWHs available through the NMOP. LMWHs are increasingly used in the outpatient sector and in some cases may be appropriately used for extended time periods (e.g., for pregnant women requiring anticoagulation). Dr. Rabie pointed out that there is now solid literature for 30 days of anticoagulation after joint replacement. While most clinicians switch patients from LMWHs to warfarin as soon as warfarin levels are therapeutic, some may opt to keep patients on enoxaparin or dalteparin for 30 days. The Committee asked the PEC to assess the opinions of providers about the necessity to have the LMWHs available through the NMOP.

10. **CONTROLLED DISTRIBUTION OF ALENDRONATE (FOSAMAX) 40 MG (FOR PAGET'S DISEASE)** – Alendronate 40 mg is no longer available through MTF pharmacies or retail network pharmacies, but is available through the NMOP. Most DoD beneficiaries who are age 65 and over cannot use the NMOP until 1 April 01. MAJ Bellemin reported that DSCP has worked out a procedure with Merck-Medco to honor prescriptions submitted by these DoD beneficiaries through their MTF pharmacies until they are eligible to use the NMOP on 1 April 01. Information about the interim procedure has been provided to the pharmacy consultants/specialty leaders for dissemination to MTF pharmacies.

11. **CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN)** – Because of specialized educational requirements mandated by the FDA, dofetilide is only available for outpatient use through Stadtlander's Pharmacy/CVS Procare (which is a non-network pharmacy for DoD beneficiaries). COL Davies reported that the 50% copay penalty for using a non-network pharmacy can be waived retroactively, but the process is cumbersome. Attempts to establish a centrally funded process for supplying dofetilide to patients have thus far been unsuccessful.

12. **CONTROLLED DISTRIBUTION OF ETANERCEPT (ENBREL)**

Although a plan to supply etanercept only through the NMOP had been contemplated, LTC De Groff reported that etanercept would continue to be available through MTF pharmacies, retail network pharmacies, and the NMOP. Immunex and Wyeth/Ayerst have allotted supplies to MTF pharmacies based on historical usage data, so MTF pharmacies (unlike retail pharmacies) are not required to submit patient enrollment numbers to obtain etanercept. DoD beneficiaries can therefore obtain etanercept from MTF pharmacies even if they did not enroll with Immunex. However, unregistered patients may experience problems if they need to obtain etanercept from a source other than an MTF pharmacy.

13. **ADJOURNMENT –** The meeting adjourned at 1200 hours. The date and location for the next meeting have not been determined. All agenda items should be submitted to the co-chairs no later than 15 April 01.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: NEWLY APPROVED DRUGS CONSIDERED FOR THE NMOP FORMULARY AND BCF

Generic name (Trade name; manufacturer)	**Indication, FDA approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Abacavir / lamivudine / zidovudine (Trizivir; Glaxo)	Approved 14 Nov 00 for use alone or in combination with other antiretroviral agents for treating HIV. Trizivir is intended only for patients whose regimen would otherwise include all three individual medications.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Sodium phosphate, dibasic, anhydrous / sodium phosphate monobasic, monohydrate (Visicol; Inkine)	Approved 21 September 2000 for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Balsalazide disodium (Colazal; Salix)	Approved 18 Jul 00 for the treatment of mildly to moderately active ulcerative colitis. Oral prodrug of 5-aminosalicylic acid (5-ASA) in which the sulfapyridine moiety of sulfasalazine has been replaced with an inert carrier molecule.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Telmisartan/ HCTZ (Micardis HCT; Boehringer-Ingelheim)	Approved 11 Nov 00 for treatment of hypertension. As a fixed-dose combination, telmisartan/HCTZ is not indicated for initial therapy.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Tacrolimus ointment (Protopic; Fujisawa)	Approved 8 Dec 00 for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis (AD) in whom the use of alternative conventional therapies is deemed inadvisable because of potential risks or in the treatment of patients who are not adequately responsive to or are intolerant of alternative conventional therapies. Indicated as 0.03% and 0.1% ointment for adults and only 0.03% ointment for children aged 2 to 15 years.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies; monitor quantities dispensed **Prior Authorization** No	Not added

APPENDIX A (CONTINUED): CONSIDERATION OF NEWLY APPROVED DRUGS FOR THE NMOP FORMULARY AND BCF

Generic name (Trade name; manufacturer)	**Indication, FDA approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Nateglinide (Starlix; Novartis)	Approved 22 Dec 00 as monotherapy in patients with type 2 diabetes mellitus whose hyperglycemia cannot be adequately controlled by diet and physical exercise, and who have not been chronically treated with other anti-diabetic agents (treatment-naïve patients). Nateglinide is also indicated for use in combination with metformin. Nateglinide may be added to but not substituted for metformin in patients already receiving metformin who still have inadequately controlled hyperglycemia. Patients receiving glyburide or sulfonylureas who have inadequately controlled hyperglycemia should not be switched to nateglinide, nor should nateglinide be added to their treatment regimen.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added

APPENDIX B: SUMMARY OF COST AVOIDANCE ASSOCIATED WITH THE NATIONAL MAIL ORDER PHARMACY (NMOP) PREFERRED DRUG PROGRAM

Summary of Switch Rates and Estimated Cost Avoidances FY 00

Non Preferred Drug	Preferred Drug	Switch Rate	Estimated Cost Avoidance	Total Attempted Provider Contacts	Estimated Cost Avoidance per Attempted Provider Contact
Cardizem CD, Dilacor XR, Cartia XT, Diltiazem XR	**Tiazac**	68%	$535,437	2904	$184
Procardia XL[1]	**Adalat CC**	53%	$313,918	1137	$276
Lodine XL, Relafen, Voltaren XR, Daypro, Naprelan	**Generic NSAIDs**	33%	$396,134	4118	$96
H2 Blockers	**Generic Ranitidine**	38%	$273,739	2485	$110
Vasotec[2]	**Zestril**	45%	$141,394	2741	$51
Famvir, Valtrex[3]	**Acyclovir**	24%	$6,783	1018	$7
Pletal[4]	**Pentoxifylline**	12%	$3424	280	$12
Ditropan XL, Detrol	**Generic Oxybutynin**	29%	$115,346	4003	$29
	Summary		**$1,779,392**	**17,668**	**$101**

Notes:

1. Calls for Procardia XL have diminished significantly (from 135 per month in Jun 00 to 7 per month in Dec 00), due to the introduction of generic equivalents for some strengths of Procardia XL. Procardia XL will be removed from the list of non-preferred drugs when generic equivalents are available for all strengths of Procardia XL.
2. Vasotec was removed from the list of non-preferred drugs when a generic equivalent became available at a competitive price in Dec 00.
3. At the May 00 meeting, the committee changed the criteria for Famvir and Valtrex so that calls would be made only for prescriptions written for chronic use (> 30 day supply). This change took effect 1 July 00.
4. Pletal was removed from the list of non-preferred drugs at the Aug 00 meeting (effective Sep 00), due to a low switch rate.

APPENDIX C: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE DOD P&T EXECUTIVE COUNCIL MEETING AND THE DOD P&T COMMITTEE MEETING

1. **BCF CHANGES**

   A. *Additions to the BCF* (See the 7 Feb 01 P&T Executive Council Minutes, Paragraph 10B and Appendix C)

      1) Clindamycin 150-mg capsules
      2) Loperamide 2-mg capsules
      3) Chlorhexidine gluconate 0.12% oral rinse (e.g., Peridex®, Periogard®, generics)
      4) Amoxicillin/clavulanic acid oral (tablets and suspension)
      5) Fluconazole oral, 150-mg tablets only. Includes only the single-dose regimen for treatment of vaginal candidiasis.
      6) Metoclopramide oral
      7) Mupirocin 1% ointment
      8) Metoprolol 50- and 100-mg oral. Does not include Toprol XL.
      9) Fluticasone oral inhaler
      10) Lactulose syrup
      11) Methotrexate oral
      12) Nitrofurantoin macrocrystals (generic equivalents to Macrodantin). Does not include Macrobid.

   B. *Changes and clarifications to the BCF* - None

2. **NMOP FORMULARY CHANGES**

   A. *Additions to the NMOP Formulary* (See Appendix A)

      1) Abacavir / lamivudine / zidovudine (Trizivir; Glaxo)
      2) Sodium phosphate, dibasic, anhydrous / sodium phosphate monobasic, monohydrate (Visicol; Inkine)
      3) Balsalazide disodium (Colazal; Salix)
      4) Telmisartan/HCTZ (Micardis HCT; Boehringer-Ingelheim)
      5) Tacrolimus ointment (Protopic; Fujisawa)
      6) Nateglinide (Starlix; Novartis)

   B. *Exclusions from the NMOP Formulary* – None

   C. *Changes to the NMOP Preferred Drug Program* (See Appendix B)

      1) Procardia XL will be removed from the list of non-preferred drugs when generic equivalents are available for all strengths of Procardia XL.

      2) Vasotec was removed from the list of non-preferred drugs when a generic equivalent became available at a competitive price in Dec 00.

3. **QUANTITY LIMIT CHANGES (NMOP AND RETAIL NETWORK) -** None

4. **CHANGES TO THE PRIOR AUTHORIZATION PROGRAM (NMOP AND RETAIL NETWORK)**

   A. A prior authorization that requires diagnostic verification of a fungal infection will be instituted for ciclopirox topical solution (Penlac Nail Lacquer) (See Paragraph 8F).

APPENDIX D: ITEMS TO BE ADDRESSED AT THE NEXT MEETING

1. *NMOP Preferred Drug Program Report* – See Paragraph 7 and Appendix B
2. *NMOP Prior Authorization Program Report* – See Paragraph 8
3. *Status of the Prior Authorization for Etanercept* – See Paragraph 8A3
4. *Status of Low Molecular Weight Heparins in the NMOP* – See Paragraph 9
5. *Controlled Distribution of Dofetilide (Tikosyn)* – See Paragraph 11
6. *Controlled Distribution of Etanercept (Enbrel)* – See Paragraph 12

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MCCS-GPE **7 Feb 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council convened at 0800 hours on 7 Feb 2001, at Ft Sam Houston, TX. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. **MEMBERS PRESENT:**

CDR Terrance Egland, MC	P& T Committee Co-chair
COL Daniel D. Remund, MS	P& T Committee Co-chair
COL Mark Nadeau, MC	Air Force (alternate)
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Matt Nutaitis, MC	Navy
MAJ Brett Kelly, MS	Army
CDR Robert Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs
LtCol Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia

MEMBERS ABSENT:

COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
CDR Kevin Cook, MSC	Navy
Joint Readiness Clinical Advisory Board Representative	

OTHERS PRESENT:

COL William Davies, MC	DoD Pharmacy Program Director, TMA
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CAPT Pat Welter	Navy Bureau of Medicine & Surgery
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
LCDR Ted Briski	TRICARE Region 9 Lead Agent Office
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
Capt Krissa Crawford, BSC	Pharmacy Practice Resident, Wilford Hall Medical Center
HM3 Cory Beckner	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
Dana Dallas	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING

The minutes were approved as written.

4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

Large budget shortfalls in the Defense Health Program jeopardize funding of the AMP program for FY 01. All AMP funds are currently "on hold" at TMA. Pharmacy will probably receive about $50 million if and when AMP funds are released. MTF pharmacies spent $12.1 million on AMP drugs in the first quarter of FY 01 (based on prime vendor data). Since expenditures for pharmaceuticals typically occur at the lowest rate during the first quarter of the fiscal year, total expenditures for AMP drugs will likely exceed $50 million in FY 01.

The Council considered a request from an MTF to add fluorodeoxyglucose (a radioactive fluoride used in positron emission tomography and single photon emission tomography) to the list of drugs covered by the AMP program. The Council denied the request because MTF expenditures for drugs currently covered by the AMP program will likely exceed the funds available for pharmacy in the AMP program.

5. NATIONAL PHARMACEUTICAL CONTRACTS

A. *Contract awards and renewals* – A joint VA/DoD single-source contract for clotrimazole 1% topical cream was awarded to Taro Pharmaceuticals with an effective date of 1 Feb 01. The joint VA/DoD single-source contract for acetaminophen 325 mg and 500 mg tablets announced at the last meeting became effective 1 Jan 01. MAJ Filby reported that the joint VA/DoD returned goods contract was awarded on 21 Jan 01 to Guaranteed Returns. LTC De Groff noted that 32 joint VA/DoD national contracts have been awarded, and approximately 25 more contracts are in various stages of development.

Information on national pharmaceutical contracts is available on the DSCP website (www.dmmonline.com).

B. *Financial impact of contracts* – COL Remund reported that the final estimate of MTF cost avoidance due to national pharmaceutical contracts was $65.2 million in FY 00, which equals 6.3% of the $1.03 billion that MTFs spent on pharmaceuticals. The weighted average percent reduction in cost for the drugs and drug classes affected by national pharmaceutical contracts was 25.3%. A summary of cost avoidance from national pharmaceutical contracts is provided in Appendix A.

C. *Status of solicitation for non-sedating antihistamine (NSA) contract* – The General Accounting Office (GAO) recently denied the only remaining protest of the solicitation for a joint VA/DoD "closed class" contract for a non-sedating antihistamine. The GAO denial of the protest opens the way for a contract to be awarded by the VA National Acquisition Center (NAC).

D. *Status of solicitation for oral contraceptive contracts* – The solicitation for joint VA/DoD single source contracts for four oral contraceptive products is scheduled to close on 23 Feb 01. The solicitation is for single sources of the following oral contraceptive products: 35 mcg ethinyl estradiol (EE) / 1 mg norethindrone; 35 mcg EE / 1 mg ethynodiol diacetate; 30/40/30 mcg EE / 0.05/0.075/0.125 mcg levonorgestrel; and 0.35 mg norethindrone.

E. *Status of potential contracting initiative for nasal corticosteroid inhalers* – DoD and VA officials will evaluate the potential for soliciting for a joint VA/DoD closed class contract for a high potency aqueous nasal corticosteroid inhaler after the VA has finished its clinical review of the drug class.

F. *Blanket purchase (BPA) agreements* – The Council wants to be more involved in the process of establishing BPAs in order to ensure that the provisions of a BPA support the Council's strategy for managing a given drug class. The Council also advocates the development of a more clearly defined process for establishing joint VA/DoD BPAs. The Council appointed a subcommittee to work on these issues. Subcommittee members are LTC De Groff, MAJ Filby, and LCDR Briski.

G. *Hepatitis A vaccine contract* – The United States Army Medical Materiel Center Europe (USAMMCE) reports that some facilities are buying Havrix instead of Vaqta, which is the contracted brand of hepatitis A vaccine. USAMMCE did not provide any information about why facilities are purchasing the non-contracted brand. The Council is unaware of any clinical reason for the facilities to use Havrix instead of Vaqta. The Council referred the issue back to DSCP for further investigation.

H. *Low molecular weight heparins* – The Council discussed the suitability of the low molecular weight heparin drug class for a contracting initiative. Additional information, including input from MTF providers, is needed to determine suitability for contracting.

6. **APPLICATIONS FOR DEA NUMBERS** – COL Humburg provided an update on online applications for DEA numbers.

7. **LEUTINIZING HORMONE RELEASING HORMONE (LHRH) AGONISTS** – A BPA makes goserelin available to MTFs at the VA national contract price in exchange for attainment of

an 80% overall share of the MTF prescriptions for LHRH agonists for prostate cancer. At the Nov 00 meeting the Council asked DSCP and the PEC to initiate an education/marketing campaign to ensure that goserelin achieves the market share required by the BPA. CAPT Torkildson reported that the following actions were taken since that meeting:

- Information regarding the Council's decision and the BPA was published in the P&T Executive Council minutes.
- Specialty leaders for Urology in each service were notified of the BPA and informed of the opportunity for cost savings. Information was forwarded to urologists.
- An article was published in the Dec 00 edition of the *PEC Update.*
- Information about the goserelin BPA was provided to the pharmacy and/or urology departments at MTFs with high leuprolide usage.

The Council reviewed MTF prescription data for LHRH agonists, but concluded that it was too early to accurately discern the effect of the BPA on LHRH agonist usage and whether MTFs are on track to achieve the 80% market share for goserelin by 1 Aug 00.

The Council was informed that DSCP recently accepted a BPA from TAP Pharmaceuticals that lowered the price of leuprolide, but still leaves leuprolide with a higher price per dose than goserelin. The Council concluded that the goserelin BPA offers the best value for the MHS. The Council reaffirmed its desire to have goserelin reach an 80% market share by 1 Aug 00 and advised the PEC to continue educational efforts to attain that goal.

8. **DRUG USAGE NOT CAPTURED IN CHCS** – As part of its analysis of LHRH agonist usage, the PEC compared the quantity of LHRH agonists purchased through the prime vendor to the quantity dispensed on outpatient prescriptions. The quantity purchased significantly exceeded the quantity dispensed at 10 MTFs. The discrepancy between the purchase data and the dispensing data is most likely due to the fact that LHRH agonists are dispensed to outpatient clinics through bulk drug orders at some MTFs. Because the agent is administered to the patient in the clinic, the drug usage is not recorded in CHCS. Outpatient drug usage that is not recorded in CHCS is omitted from clinical screening within CHCS and through the Pharmacy Data Transaction Service (PDTS). The ability of the CHCS and PDTS clinical screening processes to improve patient safety is diminished when outpatient drug usage is not recorded in CHCS. This issue was referred to LTC DeGroff, PDTS Functional Program Manager, and COL Heath, chairman of the DoD Pharmacy Board of Directors.

9. **MTF REQUESTS FOR BCF CHANGES**

   A. *Request to remove methylphenidate extended-release (Concerta) from the BCF* – An MTF requested that methylphenidate extended-release (Concerta) be removed from the BCF because:

   - They could find no literature to indicate that Concerta is a superior product to those already available.
   - Concerta is not the only agent that can be dosed prior to the child leaving for school without requiring a noon dose.
   - Having another Schedule II item is always an issue.

According to a recent New Product Bulletin from the American Pharmaceutical Association (APhA), the duration of action is about 12 hours for Concerta, compared to 3 to 6 hours for methylphenidate immediate-release tablets and about 8 hours for the sustained release tablets. To the extent that a longer duration of action is desirable, Concerta might be considered superior to other currently available methylphenidate products.

A PEC analysis of MTF prescriptions for a random sample of patients under the age of 18 who received more than one prescription for sustained-release methylphenidate during FY 00 revealed the following:

- 60% (116/193) of the patients received another medication for ADHD in addition to sustained-release methylphenidate.
- 40% (78/193) of the patients were prescribed a midday dose of either sustained-release methylphenidate or another medication for ADHD.

Although methylphenidate sustained release tablets should theoretically obviate the need for a midday dose, MTF prescription data show that midday doses are frequently prescribed for patients taking methylphenidate sustained release tablets. The Council voted to keep Concerta on the BCF.

B. *Request to add gatifloxacin (Tequin) and remove levofloxacin (Levaquin) from the BCF* – An MTF pharmacy chief suggested that the addition of levofloxacin to the BCF may have been based on (1) an incorrect price for gatifloxacin, and (2) inadequate consideration of *S. pneumoniae* MICs and use in sexually transmitted diseases.

The Council was aware at the Nov 00 meeting that both levofloxacin and gatifloxacin were available for $2.00 per daily dose through BPAs. The Council also considered levofloxacin and gatifloxacin to be very similar in safety, tolerability and efficacy. Levofloxacin accounted for nearly 70% of all fluoroquinolone prescriptions dispensed at MTFs, while gatifloxacin accounted for less than 1% of fluoroquinolone prescriptions.

As requested by the Council, DSCP obtained a revised BPA that makes it easier for MTFs to obtain levofloxacin at the BPA price. The revised BPA offers levofloxacin 250 mg and 500 mg to all MTFs at an upfront price of $2.00 per tablet. Continuation of the BPA price is contingent upon levofloxacin achieving either (1) an 80% aggregate DoD market share within 6 months, or (2) a 50% market share at individual MTFs. Market share will be based on patient days of therapy and will be calculated from USPD prescription data.

The revised BPA achieves the objective of making it easier for MTFs to obtain levofloxacin at the BPA price, since MTFs are no longer responsible for individually monitoring drug usage to meet market share requirements. In addition, use of prescription data eliminates the problem of prime vendor purchases of ciprofloxacin being included in the denominator for calculating levofloxacin market share. However, some of the provisions in the BPA were unacceptable to the Council. The Council asked DSCP to revise the BPA to eliminate the unacceptable provisions.

The Council was also informed that a new incentive price agreement offers gatifloxacin to MTFs at a price of $1.90 per daily dose. The incentive price is contingent on gatifloxacin having a preferred or co-preferred formulary position at an individual MTF.

The Council voted to keep levofloxacin on the BCF. The fluoroquinolone class remains open on the BCF, so MTFs may have other fluoroquinolones on their formulary in addition to levofloxacin.

C. *Request to remove divalproex ER (Depakote ER) from BCF* – An MTF pharmacist asserted that Depakote ER (which is dosed once daily) offers no advantages over Depakote (which is dosed twice daily) because there are no data to prove better compliance.

All oral dosage forms and strengths are generally included for a drug listed on the BCF. The DoD P&T Committee may specifically omit a dosage form or strength from the BCF if it is excessively expensive compared to the other dosage forms/strengths, or if impending availability of a generic equivalent makes it inadvisable to include a given dosage form. Depakote ER is priced essentially the same as Depakote. The Council voted to keep Depakote ER on the BCF.

10. **BASIC CORE FORMULARY REVIEW**

A. *BCF overview and analysis* – The Council reviewed the objective of the BCF and factors that are considered in selecting drugs for the BCF (see Appendix B). The PEC recommended drugs for addition to the BCF based on the following information and analyses:

1) An analysis of USPD data showed that 72.6% of the prescriptions filled at MTF pharmacies in FY 00 were filled with drugs that were on the BCF at the end of FY 00. Prescriptions for most over-the-counter drugs were excluded from the analysis because they generally are not eligible for inclusion on the BCF. The analysis did not characterize second-generation antihistamines, low molecular weight heparins, leukotriene antagonists, and estrogenic vaginal creams as BCF drugs—even though the BCF requires MTFs to have at least one agent from each of those drug classes on the MTF formulary.

2) A frequency distribution of prescriptions filled at MTFs for BCF and non-BCF drugs that was generated from USPD data.

3) A survey of MTFs to determine the MTF formulary status for 98 drugs that are not currently included on the BCF.

4) Input from MTF providers.

5) Drug usage and cost trends from prime vendor and USPD data.

B. *Addition of drugs to the BCF* – The Council was forced to take a conservative approach in adding drugs to the BCF because of the uncertain funding situation for the Defense Health Program in FY 01. The Council added 12 drugs to the BCF, which are listed in Appendix C. [NOTE: A comprehensive list of all BCF and NMOP formulary changes is provided in an appendix to the 8 Feb 01 DoD P&T Committee minutes.]

C. *Drugs not added to the BCF* – The Council considered clinical information and usage data regarding gabapentin, COX-2 inhibitors, and dihydropyridine calcium channel blockers. The Council did not add any of these drugs to the BCF.

D. *Ongoing review* – The PEC is reviewing topical corticosteroids, benzodiazepines, and medications for acne and overactive bladder. Information on these drugs will be presented at the next meeting of the P&T Executive Council.

E. *Status of lancets on the BCF* – A Council member asked why lancets are not included on the BCF. The Council tabled this issue until the next meeting.

11. The meeting adjourned at 1230 hours. The date and location of the next meeting are to be determined.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

Appendix A: Cost Avoidance in DoD MTFs Due to National Pharmaceutical Contracts, FY 00

Estimated Cost Avoidance in DoD MTFs Due to National Pharmaceutical Contracts, Fiscal Year 2000

Drug/Drug Class	Contract Start Date	Weighted Average Price/Unit Before Contracted	Theoretical FY 00 Cost If Not Contracted	FY 00 Actual Cost	Cost Avoidance	Percent Reduction in Cost
Statins	1-Oct-99	$0.961874	$94,988,500	$72,672,448	$22,316,052	23.49%
PPIs	1-Oct-99	$1.681407	$97,608,455	$78,179,686	$19,428,769	19.90%
Lisinopril	1-Aug-99	$0.284396	$22,410,939	$12,338,214	$10,072,726	44.95%
Diltiazem	15-Dec-98	$0.631469	$13,077,589	$6,118,739	$6,958,850	53.21%
Ranitidine	16-Nov-98	$0.066602	$3,819,158	$1,956,040	$1,863,118	48.78%
Hepatitis A	18-Sep-99	$16.981597	$8,221,080	$6,546,563	$1,674,517	20.37%
Albuterol	16-Nov-98	$3.297032	$2,882,500	$1,932,971	$949,529	32.94%
Timolol Gel	14-Jan-00	$14.598153	$952,836	$417,571	$535,265	56.18%
Verapamil	20-Aug-99	$0.125912	$2,358,022	$1,804,406	$553,616	23.48%
Cimetidine	16-Nov-98	$0.072763	$833,304	$540,391	$292,913	35.15%
Terazosin	5-Sep-00	$0.459093	$726,193	$539,565	$186,628	25.70%
Captopril	18-Oct-99	$0.036173	$313,233	$171,569	$141,664	45.23%
Nortriptyline	15-Oct-99	$0.049281	$311,276	$227,111	$84,165	27.04%
Gemfibrozil	1-Jan-00	$0.077935	$995,172	$914,650	$80,522	8.09%
Naproxen	3-Jul-00	$0.069829	$752,114	$673,203	$78,911	10.49%
Amoxicillin	7-Aug-99	$0.040549	$560,140	$499,419	$60,721	10.84%
Insulin Syringes	1-May-00	$0.098121	$430,084	$408,406	$21,678	5.04%
Timolol Drops	14-Jan-00	$2.795264	$195,968	$162,419	$33,548	17.12%
Nicotine Patches	1-Jun-00	$2.567746	$518,454	$460,290	$58,163	11.22%
Levobunolol	14-Jan-00	$4.641527	$54,385	$37,522	$16,863	31.01%
Fluocinonide	1-Sep-99	Cream $1.816402 Oint $6.210282 Sol $6.422653	$370,547	$355,800	$14,747	3.98%
Prazosin	1-Nov-99	$0.032916	$132,685	$118,531	$14,153	10.67%
Amantadine	28-Aug-99	$0.063871	$61,008	$53,950	$7,058	11.57%
Naproxen Sodium	3-Jul-00	$0.073176	$47,017	$48,695	($1,678)	-3.57%
Salsalate	15-Mar-00	$0.026462	$79,751	$87,525	($7,774)	-9.75%
Insulin	1-Nov-99	$5.292812	$4,818,894	$5,071,036	($252,142)	-5.23%
Acyclovir	1-Oct-00	$0.121623			NA	NA
Azathioprine	1-Oct-00	$0.477152			NA	NA
Hydroxyurea	1-Oct-00	$0.295324			NA	NA
Pentoxifylline	1-Oct-00	$0.182262			NA	NA
Rifampin	1-Oct-00	$0.566776			NA	NA
Sucralfate	1-Oct-00	$0.198476			NA	NA
Acetaminophen	1-Jan-01				NA	NA
TOTAL FY00			**$257,519,303**	**$192,336,719**	**$65,182,584**	**25.31%**

Explanation of Cost Avoidance Calculations: Cost avoidance equals the difference between (1) the theoretical cost that would have occurred in FY 00 if a contract had not existed, and (2) the actual cost that was incurred in FY 00 for the "market basket" of drugs that pertains to each contract. The theoretical cost that would have occurred in FY 00 if a contract had not existed was estimated by multiplying the weighted average price/unit that existed before the contract took effect by the quantity purchased in FY 00 after the contract was in effect. The "market basket" of drugs includes both the contracted and the non-contracted drugs that pertain to a given contract. For example, the cost avoidance for statins takes into account the expenditures for all six statins, not just the two contracted statins.

Appendix B: Objective of the Basic Core Formulary and Factors Considered in Drug Selection

A. *Objective of the Basic Core Formulary (BCF)*

Ensure uniform availability of cost-effective pharmaceuticals at MTF pharmacies to meet the majority of patients' primary care needs

B. *Selecting drugs for the BCF*

Compare the drug to other agents in the class or other agents that are used for a given disease/condition, based on the following factors:

Safety

Tolerability

Efficacy / Effectiveness

Price / Cost

Other factors, including but not limited to:

- Place in therapy / clinical niche
- Interchangeability of drugs in the class
- Variability in patient response to drugs in the class
- MTF provider opinions/preferences
- Market share trends within the drug class
- Percentage of MTFs that have the drug on formulary
- Potential for inappropriate use
- Patent expirations and impending availability of generic equivalents

Appendix C: Drugs Added to the BCF

Drug	Factors Considered Safety, tolerability, efficacy, price, and other factors (STEPO) relative to other drugs in the same class and/or current BCF items, if any	Percentage of MTFs reporting drug on formulary
Clindamycin 150-mg capsules	S/T/E: Safe and effective for treatment of commonly encountered acute infections. P: Generics available. Capsule prices range from $0.28 to $1.15 (branded 300-mg capsule) O: Class not represented on current BCF. Alternative for skin, soft-tissue, and respiratory tract infections in PCN allergic patients. Needed for treatment of polymicrobial infections where anaerobes are suspected.	Unknown
Loperamide 2-mg capsules	S/T: Safer than diphenoxylate/atropine (e.g., Lomotil). Does not interact with MAO inhibitors or CNS depressants. Does not cause physical dependence. Less drowsiness and sedation compared to diphenoxylate/atropine. E: Efficacy similar to diphenoxylate/atropine. P: DAPA price = $0.046 per capsule, compared to $0.017 per tablet for diphenoxylate/atropine O: Available on a high number of local formularies. A non-scheduled alternative to diphenoxylate/atropine (will not add to administrative burden).	98.7% (155/157)
Chlorhexidine gluconate 0.12% oral rinse (Peridex®, Periogard®, generics) – used for treating gingivitis	S/T: No systemic effects (topical application). Potential cosmetic concerns include staining of the tooth surfaces, restorations, and dorsum of the tongue. Occasional alterations in taste perception. E: No available published literature that treating gingivitis decreases tooth loss. There are conflicting reports on the relationship between periodontal disease and coronary heart disease in men. P: Price ranges from $2.44 to $3.00 for 473 mL bottles O: No similar agents are available on the BCF Satisfies an unique therapeutic niche Dental consultants agreed that this product belongs on the BCF Space limitations may be a concern in smaller MTFs	96.8% (152/157)
Amox/clav (Augmentin) tablets and suspension	S/T/E: Widely used agent proven safe and effective in broad range of infectious processes. P: Already available at nearly all MTFs, so minimal cost impact. O: Class not represented on BCF. Widely used to treat respiratory tract infections and otitis media where penicillinase-producing organism is known or suspected.	Tablets - 96.8% (152/157) Susp – 97.5% (153/157)
Fluconazole oral, 150-mg tablets only	S/T/E: Proven safe and effective for treatment of vaginal candidiasis. P: $6.63 to $6.89 per treatment. OTC cream DAPA price range from $3.35 to $4.42 per 45gm tube. O: No alternatives currently listed on the BCF. As effective as OTC vaginal creams. Offers advantage of single dose therapy and ease of administration.	96.8% (152/157)

Drug	Factors Considered Safety, tolerability, efficacy, price, and other factors (STEPO) relative to other drugs in the same class and/or current BCF items, if any	Percentage of MTFs reporting drug on formulary
Metoclo-pramide oral	S/T: Metoclopramide is well tolerated with CNS side effects of drowsiness, fatigue and lassitude occurring in roughly 10% of patients at normal doses. Extrapyramidal and/or dystonic reactions are rare, occurring in about 0.2% of patients. E: Effective in the treatment of diabetic gastroparesis for which there is no other treatment. P: Price is less than $0.01 per tablet. O: No similar product on the BCF	Metoclopramide 95.5% (150/157)
Mupirocin 1% ointment	ST: Only safety issue would be in patients with renal failure who need to use it on a large open wound area; otherwise mupirocin is not absorbed systemically. No significant tolerability issues. E: Bacitracin nearly 100% failure rate for impetigo. Oral erythromycin now > 50% failure rate due to resistance. Nearly 100% successful treatment of impetigo with mupirocin or cephalexin. Using mupirocin avoids problems related to systemic therapy. Studies were done at Tripler. P: DAPA prices: ointment $22.03 per 22gm tube; cream $16.24 per 15 gm tube, $27.56 per 30 gm tube; nasal ointment $29.57 (box of 10, 1gm tube) O: Nothing similar in this category of therapy on BCF. On the VA formulary with restrictions. Many schools and day care centers will not allow children with impetigo to return until they have been treated.	Mupirocin oint. – 143/157 – 91.1%
Metoprolol 50mg, 100mg oral (Toprol XL is not included in this listing for metoprolol)*	S: Safe when used as directed. Avoid in patients with severe reactive airway disease, concurrent negative inotropic agents, severe or unstable heart failure. T: Well tolerated. β-1 selective agent may minimize β2 blockade related adverse effects (bronchospasm). Selectivity is lost with higher doses. E: Effective in treating HTN, angina, post-MI, selected CHF patients (stable NYHA II and NYHA III). Proven mortality benefit in all these conditions. Usually dosed BID. Can be used QD for HTN in some patients. P: Inexpensive. Metoprolol 50mg generic - $0.02-0.06, Metoprolol 100mg generic - $0.03-0.05, Toprol XL® 50mg - $0.46, Toprol XL® 100mg - $0.92 (Dec 2000 DAPA prices). Toprol XL® 25mg scored tablet – submitted for FDA approval for stable NYHA II-III CHF patients – release date unknown. O: Proven mortality benefit in several indications. Want to encourage use, esp in post-MI patients (decreases mortality and is a HEDIS measure). **Toprol XL® was excluded because there are insufficient clinical advantages to justify the incremental cost compared to immediate release metoprolol.*	Metoprolol – 142/157 – 90.4% Toprol XL – 7/157 – 4.5%

Drug	Factors Considered Safety, tolerability, efficacy, price, and other factors (STEPO) relative to other drugs in the same class and/or current BCF items, if any	Percentage of MTFs reporting drug on formulary
Fluticasone oral inhaler (For complete analysis and clinical information, see Review of Orally Inhaled Corticosteroids, Nov 00 DOD P & T Committee Meeting)	S/T: Fluticasone is equal in safety to other inhaled corticosteroids (ICS) on the market. Adverse reactions appear to be similar to the other available ICS. E: When given in equipotent doses, all the ICS appear to have equal efficacy. Fluticasone, like budesonide, is a high potency ICS that may require fewer puffs per day to achieve control of asthma. P: DAPA prices - 44 mcg MDI $19.88 110 mcg MDI $29.03, 220 mcg MDI $50.65, 50 mcg DPI $21.32, 100 mcg DPI $27.95, 250 mcg DPI $35.98 O: There are no high potency ICS on the BCF. Of the two high potency ICS, fluticasone has a significant share of the market compared to budesonide (39% versus 3.5%). The two high potency ICS are not interchangeable. Budesonide is a dry powder inhaler (DPI); fluticasone is available as both a DPI and a metered dose inhaler (MDI). Given the difference in dosage forms, significant and costly patient education would be required to switch patients currently on fluticasone to budesonide. Budesonide is less desirable than fluticasone because providers report that patients have difficulty in administering the correct dose because of the lack of tactile feedback. Breath actuation with budesonide may be particularly difficult for children.	135/157 (86.0%)
Lactulose syrup	ST: No significant safety issues. Better tolerated than other 2 maintenance therapies recommended for children (mineral oil, magnesium salts). Common side effects (flatulence, belching, abdominal distension, abdominal pain) generally mild. E: Several clinical trials have demonstrated significant increase in stool frequency, weight, volume, and water content compared to placebo. P: DAPA price $3.97/480 ml vs. $17.92 approximate retail price O: Constipation prevalent in pediatric population. Adult therapies not generally used in children	Unknown
Methotrexate oral	ST: Substantial toxicity, low therapeutic index. Not possible to logically compare to other agents. E: No equivalent antineoplastic agent on BCF. No other DMARDs on BCF. Efficacy as antineoplastic agent and immunosuppressive agent clearly demonstrated. P: Generic product available. DAPA price $0.12/tablet; 2.5-10 fold lower than approximate retail price O: Availability of best alternative DMARD (etanercept) greatly limited. Rheumatrex dose packs significantly more expensive than bulk tablets.	80.9% (127/157)

Drug	Factors Considered Safety, tolerability, efficacy, price, and other factors (STEPO) relative to other drugs in the same class and/or current BCF items, if any	Percentage of MTFs reporting drug on formulary
Nitrofurantoin macrocrystals (generic equivalents to Macrodantin) Macrobid is not included*	S/T/E: Specifically for the treatment and suppression of UTI. P: Generics available Price range from $0.07 to $0.87/dose. O: Recommended as one of primary agents in DOD Acute Dysuria or Urgency in Women Guideline. **MacroBid â was excluded because it offers no significant clinical advantage over available generic products.*	Capsules – 72.6% (114/157) Macrocrystals – 79% (124/157) Susp - Unknown

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Pharmacoeconomic Center

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MCCS-GPE **16 NOV 00**

MEMORANDUM FOR: Executive Director of Tricare Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. A meeting of the DoD P&T committee convened at 0800 hours on 16 November 2000, at Ft Sam Houston, TX.

2. **MEMBERS PRESENT:**

CDR Terrance Egland, MC	Co-chair
COL Daniel D. Remund, MS	Co-chair
LTC Judith O'Connor, MC	Army
MAJ Brett Kelly, MS	Army
CDR Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert Rist	Coast Guard
LTC Greg Russie	Joint Readiness Clinical Advisory Board
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Ron Mosier	Department of Veterans Affairs
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services

MEMBERS ABSENT:

COL Rosa Stith, MC	Army

OTHERS PRESENT:

CAPT Joe Torkildson	DoD Pharmacoeconomic Center
COL Mike Heath, MS	Army Pharmacy Consultant, DoD Pharmacy Board of Directors
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
LTC (P) William Davies	DoD Pharmacy Program Director, Tricare Management Activity (TMA)
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC Steven Humburg	Health Affairs
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
LCDR Mark Richerson	DoD Pharmacoeconomic Center
MAJ Barbara Roach, MS	DoD Pharmacoeconomic Center
MAJ Ed Zastawny	DoD Pharmacoeconomic Center
HM3 Cory Beckner	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Howard Altschwager	Deputy General Counsel, TMA
David Chicoine	Uniformed Services Family Health Plan
Eugene Moore	DoD Pharmacoeconomic Center
Jeremy Johnson	Family Practice Pharmacy Resident, University of Texas Pharmacy Program
Mark Petruzzi	Merck-Medco
Elizabeth Scaturro	Merck-Medco
Carol Scott	DoD Pharmacoeconomic Center
David Spiler	Merck-Medco
Shana Trice	DoD Pharmacoeconomic Center
Vincent Valinotti	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Eric Vetter	Pharm.D. Student, Ferris State University

ADMINISTRATIVE ISSUES

The minutes from the last meeting were corrected as below:

- The heading for Paragraph 11G was changed to "General Accounting Office (GAO) Report—Review of Drug Classes for Contracting Potential."

- Paragraph 16 (Formulary Controls in the Retail Pharmacy Network) was revised to delete the sentence "MCSCs can not currently impose prior authorizations beyond those approved by the DoD P&T committee."

3. **REVIEW OF INTERIM DECISIONS –** The co-chairs reported on the following interim decisions, which were confirmed by the committee:

- Quantity limit for testosterone gel (Androgel) – The normal quantity limit for a Schedule III drug would be a 30-day supply. An exception was made to allow prescriptions for Androgel to be filled for up to a 90-day supply, based on its chronic use and the lower potential for overuse compared to other testosterone formulations.

- Coverage of perindopril (Aceon; Solvay) through the National Mail Order Pharmacy (NMOP) program – Perindopril was approved in 1993, but only recently marketed. Perindopril was added to the NMOP Formulary.

- The co-chairs decided to establish and have the first meeting of the DoD Executive Council as a separate committee composed solely of federal employees. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to a pharmacy benefits program and providing other direction and assistance to the P&T committee. The first meeting of the DoD Executive Council was held 15 Nov 00. Minutes of the meeting will be posted on the PEC website.

4. **PROCEDURE FOR REQUESTING BCF CHANGES** – At the last meeting, the committee appointed a subcommittee to develop standard procedures for MTFs to request changes to the Basic Core Formulary (BCF) and to propose agenda items for the DoD P&T Committee. MAJ George Jones presented findings of the subcommittee, including a proposed form to be placed on the PEC website to facilitate requests from MTF providers and other DoD personnel for additions, deletions, or changes to the BCF.

   Some committee members said that requests for BCF changes should be routed through the MTF or regional P&T committee rather than being submitted directly to the DoD P&T committee by an individual provider. Other committee members said that providers would view that as a "roadblock" to submitting requests. The committee voted not to require submission through the MTF or regional P&T committees. The committee asked the PEC to revise the draft form as necessary and place it on the PEC website. Use of the form will be reviewed in 3 to 6 months.

5. **IMPLEMENTATION OF FY00 AND FY01 NATIONAL DEFENSE AUTHORIZATION ACTS** – LTC Davies briefed the committee on the ongoing efforts to implement the provisions of the FY00 and FY01 National Defense Authorization Acts pertaining to the Uniform Formulary and the DoD P&T Committee.

6. **LINEZOLID USAGE IN THE RETAIL NETWORK** – The managed care support contractors (MCSCs) reported that linezolid usage had been minimal and appears appropriate. The committee agreed that a prior authorization is not necessary and closed the issue.

7. BCF AND NMOP FORMULARY ISSUES

A. The committee considered the eighteen newly approved drugs listed in Appendix A. For each drug, the committee determined status on the NMOP Formulary; the necessity for NMOP or retail network formulary restrictions (NMOP Preferred Drug Program, quantity limits, or prior authorization); and status on the BCF.

B. *Mifepristone (Mifeprex, RU-486; Danco Labs)*, approved 28 Sep 00 for medical termination of intrauterine pregnancy, through day 49 of pregnancy. Because the drug will only be available via direct shipment to qualified providers and because of existing DoD policies regarding termination of pregnancy, mifepristone was excluded from the NMOP and will not be a covered benefit through network providers. COL Davies addressed the issue of how mifepristone will be incorporated into existing medical care directives in the MTFs. He stated that TMA and Health Affairs is working on a policy to clarify the distribution of mifepristone and the processes that will need to be followed to obtain the drug. He stated that although there are potential uses for mifepristone other than termination of pregnancy, availability of the drug is likely to be limited by the FDA-approved indication and distribution process.

8. **NON-PREFERRED/PREFERRED DRUG PAIRS IN THE NMOP** – CDR Mark Brouker reported that the report could not be prepared because the data were not available.

9. PRIOR AUTHORIZATIONS

A. *Cost analysis of NMOP prior authorizations (PAs)* – Shana Trice (PEC) reported on the cost analysis of prior authorizations in the NMOP, using the same model presented at the Aug 00 meeting. For each drug, the costs that would be incurred for 1000 new prescriptions submitted to the NMOP that are subject to the PA process were compared to the costs that would be incurred if the prescriptions were not subject to the PA process. The analysis takes into account the cost of drug therapy, the charge from Merck-Medco for performing the PA, the estimated number of refills associated with each new prescription and the estimated cost of alternative therapy for prescriptions not filled as a result of the PA process. The analysis does not quantify the "sentinel effect" of PAs (i.e., the possibility that providers prescribe the drug less frequently because they know the drug is subject to prior authorization).

The analysis showed that total costs for each drug would be higher without PA than they are with PA. The cost avoidance resulting from the PA process is shown in the following table:

Drug	Cost avoidance per new Rx submitted
Etanercept (Enbrel)	$111.86
Sildenafil (Viagra)	$26.46
COX-2 inhibitors	$18.56

Although preliminary information on the PA for antifungals for onychomycosis (terbinafine and itraconazole) was presented, the committee agreed that it is too soon to draw any meaningful conclusions.

B. *Status of changes in prior authorization criteria for etanercept and COX-2s* – The changes in criteria for etanercept and COX-2s discussed at the February and August meetings have been completed, with the exception of the revision of the COX-2 PA to reflect approval of celecoxib for familial adenomatous polyposis (FAP). This change is in progress.

C. *Revision of prior authorization forms to reflect the rationale for the prior authorization* – The PA forms on the PEC website, which are mailed in by beneficiaries with their prescriptions after being completed by prescribers, have been changed to include the clinical rationale for the prior authorization. Merck-Medco is in the process of adding the clinical rationale language to the forms it faxes to prescribers.

D. *Proposal to increase the length of time for which etanercept is approved* – The committee considered a proposal to increase the length of time for which etanercept PAs are approved from one year to five years, which is Merck-Medco's current standard for etanercept in other health plans. Reports of rare cases of demyelinating disorders and pancytopenia in patients receiving etanercept engendered concern on the part of committee members about lengthening the approval period. The committee decided not to make any changes to the etanercept PA at this time.

E. *Proposal to change the COX-2 PA to reflect findings of the Celecoxib Long-term Arthritis Safety Study (CLASS)* – For patients taking aspirin in the CLASS study, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers were not significantly different for celecoxib versus NSAIDS. These results indicate that celecoxib confers no GI safety benefit over NSAIDs for patients who take aspirin for cardioprotection. The PA criteria for COX-2 inhibitors may need to be revised so that usage of COX-2 inhibitors is not approved for patients who take aspirin for cardioprotection. The committee asked the PEC to further evaluate the consequences and costs of making such a change in the COX-2 PA criteria.

10. NMOP AND RETAIL NETWORK QUANTITY LIMITS

A. *Report of the subcommittee on quantity limits for proton pump inhibitors (PPIs)* – Bill Hudson (Humana) reported that the subcommittee considered two clinical questions 1) is there undetected disease that is being masked by chronic PPI therapy, and 2) do people really need long-term therapy with these drugs? With the assistance of expert opinion, the subcommittee concluded that there is probably very little undetected disease masked by PPI use. They also concluded that a substantial number of patients do need some type of long-term therapy, although many of these patients could be managed with a H2 blocker such as ranitidine instead of a PPI. The committee decided not to institute specific quantity limits for the PPIs in the NMOP and retail network.

B. *Quantity limits for isometheptene 65 / dichloralphenazone 100 / acetaminophen 325 mg oral (Midrin, generics)* – Because the status of this combination drug is being changed to

Schedule IV and because it is used for migraine treatment, the question arose as to whether quantity limits for the NMOP and retail network should be specified. However, the drug has different limits for different indications—5 capsules per day for migraines and 8 capsules per day for tension headaches—and it is difficult to determine how many capsules patients are likely to use on a monthly basis. The committee concluded that there is no need to have a specific quantity limit for this drug, since no specific limits are set for other scheduled medications. A clinical maximum for all drugs set by First Data Bank will apply across the MHS as the Prescription Data Transaction Service (PDTS) is implemented. Like other Schedule III - V drugs, isometheptene/dichloralphenazone/acetaminophen will be limited to a 30-day supply with 5 refills in the NMOP.

C. *Quantity limits for sumatriptan (Imitrex) 100 mg* – This is a newly approved dosage form of sumatriptan. The committee agreed with the proposed quantity limits of 27 tablets per 90 days in the NMOP and 9 tablets per 30 days in the retail network, which are consistent with quantity limits for other strengths of sumatriptan. Sumatriptan 100 mg tablets are packaged in 9's.

11. **CONTROLLED DISTRIBUTION OF ALENDRONATE (FOSAMAX) 40 MG (FOR PAGET'S DISEASE)** – Nationally, this dosage strength of alendronate will only be available from one specialty pharmacy (CVS ProCare). LTC Don De Groff reported on efforts to work out distribution within DoD. He reported that the manufacturer (Merck), DSCP, Merck-Medco, and the NMOP wholesaler have worked out the payment issues to allow DoD beneficiaries to go through the NMOP to process their prescriptions rather than dealing with CVS ProCare. DoD patients will receive a business reply card for Merck's Paget's Patient Support Program, giving them access to this program if they wish to participate. The PDTS Customer Service Support Center (CCSC) will assist in redirecting DoD beneficiaries receiving prescriptions through the retail pharmacy network to the NMOP in order to centralize the program. LTC De Groff emphasized that it is important that all MTF prescriptions for alendronate 40 mg, including new prescriptions, be filled at the NMOP because alendronate 40 mg will no longer be available to MTFs as of 15 Dec 00. More information will be supplied by DSCP and/or the PEC as soon as possible, and will be posted on the DSCP website. This program is expected to affect approximately 300 patients DoD-wide.

    The committee agreed that the BCF requirement for alendronate should be clarified to exclude the 40-mg tablet, since it will not be available at MTFs. The 40-mg tablet will remain on the NMOP Formulary, since the NMOP will be providing the drug.

12. **CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN)** – Because of specialized educational requirements mandated by the FDA, this drug is only available for outpatient use through a single specialty pharmacy in the U.S. (Statlander's Pharmacy/CVS Procare). LTC Don De Groff reported that while the issue of payment for the medication is not yet entirely worked out, the communication procedures to support clinical monitoring have been defined. All prescriptions for dofetilide for DoD beneficiaries received by CVS Procare will be reported to the PDTS Customer Service Support Center (CCSC) (using a flat file in NCPDP compliant format) on a daily basis and a paper claim will be entered by the CSSC so that any positive prospective DURs (e.g., drug interactions) can be reported to CVS Procare. More information

concerning distribution and payment will be supplied by DSCP as soon as the issues are resolved.

13. **CONTROLLED DISTRIBUTION OF ETANERCEPT (ENBREL) –** The manufacturer of etanercept (Immunex) very recently reported that production of etanercept is at maximum capacity and that demand will likely exceed supply until new production facilities are constructed. In order to ensure that patients currently receiving etanercept are able to continue therapy, Immunex is setting up an process requiring existing patients to enroll by 1 Jan 01. Further details are available from Immunex at *www.enbrelenrollment.com*.

    The etanercept enrollment and distribution process is likely to be very difficult in DoD facilities because of the multiple chains of distribution through which MTF pharmacies obtain products. LTC Don De Groff reported on discussions with Immunex and Wyeth-Ayerst (co-marketer of Enbrel) to attempt to establish a process for DoD patients to use the NMOP only to obtain supplies of etanercept. The program start of 1 Jan 00 will not be enforced for DoD beneficiaries obtaining etanercept through the NMOP or MTFs, pending resolution of this issue.

14. **PUBLIC HEALTH ADVISORY FROM THE FDA REGARDING PHENYLPROPANOLAMINE (PPA) –** The committee discussed the recent advisory from the FDA stating that the agency is taking steps to remove PPA from all drug products and requesting that drug companies discontinue marketing products containing PPA, based on the evidence of an association between PPA and hemorrhagic stroke. Although the risk of hemorrhagic stroke is very low, the FDA is advising patients to stop taking products containing PPA. USAMMA has sent out two medical material quality control messages informing MTFs of the FDA advisory and advising pharmacies to stop dispensing the drug.

    The committee removed guaifenesin /PPA (e.g., Entex LA) from the BCF. The committee did not select an alternative agent for the BCF at this meeting because of anticipated reformulation of products by manufacturers and because the selection will be addressed as part of the BCF review to be addressed at the Feb 01 meeting.

15. **ADJOURNMENT –** The meeting adjourned at 1415 hours. The next meeting will be held in February 01 at a date and location to be determined. All agenda items should be submitted to the co-chairs no later than 15 Jan 01.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

List of Appendices

APPENDIX A: CONSIDERATION OF NEWLY APPROVED DRUGS FOR THE NMOP FORMULARY AND BCF

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Metformin/ glyburide tablets (Glucovance; Bristol-Myers Squibb)	Approved 31 July 00 for initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia can not be satisfactorily managed with diet and exercise alone; and second-line therapy when diet, exercise and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added. While Glucovance is slightly less costly than Glucophage at the moment, generic metformin is expected to become available sometime around July 2001, presumably at a greatly decreased cost. The committee agreed that the combination therapy did not appear to offer enough additional benefit to offset the potential for higher costs compared to generic metformin and generic glyburide, as well as the loss of dosing and titration flexibility compared to the individual components.
Metformin extended release tablets (Glucophage XR; Bristol-Myers Squibb)	Approved 13 Oct 00 as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes; may be used concomitantly with a sulfonylurea or insulin to improve glycemic control (same indication as immediate release metformin).	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Excluded from the BCF listing for metformin. MTFs are not required to have Glucophage XR on their formularies, but may add it if they so desire. While Glucophage XR 500 mg is slightly less costly than Glucophage 500 mg at the moment, generic metformin is expected to become available sometime around July 2001, presumably at a greatly decreased cost. The committee agreed that extended release preparation did not appear to offer enough additional benefit to offset the potential for higher costs compared to generic metformin, when available.
Alendronate 35- and 70-mg (once weekly) tablets (Fosamax; Merck)	Approved 20 Oct 00 for prevention (35-mg tablet) or treatment (70-mg tablet) of osteoporosis in postmenopausal women	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Listing for alendronate on the BCF will include the once-weekly formulations. Once weekly administration appears to be as effective as once daily and may have tolerability/safety advantages. The cost per week for the once-weekly and once-daily tablets is the same. The earliest patent expiration listed in the FDA Orange Book for alendronate is 2007.

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Divalproex sodium ER tablets (Depakote ER; Abbott)	Approved 13 Oct 00 for prophylaxis of migraines in adults	Added	**NMOP Preferred Drug Program** No	Listing for divalproex sodium on the BCF will include Depakote ER. Depakote ER is only indicated for prophylaxis of migraine headaches, while delayed release divalproex sodium (Depakote) is indicated for seizure disorder, bipolar disorder, and prophylaxis of migraine headaches. Depakote ER may have some convenience advantages (two 500-mg tablets once daily as opposed to one 500-mg Depakote tablet twice daily) and is cost-neutral. The earliest patent expiration listed in the FDA Orange Book for Depakote is 2008.
			Quantity Limits General rule applies	
			Prior Authorization No	
Methyl-phenidate HCl extended release tablet (Concerta; Alza)	Approved 1 Aug 00 for the treatment of attention deficit disorder	Added	**NMOP Preferred Drug Program** No	The BCF listing for methylphenidate will include Concerta. Concerta is given once daily. It consists of an immediate release component and an extended release component, which provides for initial morning efficacy followed by extended release of medication over an approximately 12-hour period. At $1.30 - $1.38 per day, Concerta is approximately 57% more costly than a typical regimen of extended-release plus immediate release methylphenidate. However, once daily dosing of Concerta has the potential to obviate the need for children to take doses during the school day. The committee pointed out that this is a quality of life issue that has a direct impact on active duty dependents and active duty personnel.
			Quantity Limits NMOP: 90 day supply Retail: 30 day supply or 90 day supply with 3 co-pays	
			Prior Authorization No	

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Tinzaparin injection (Innohep; Dupont)	Approved 18 Jul 00 for treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. Safety and effectiveness were established in hospitalized patients.	Not added. The low molecular weight heparins (LMWHs) are not currently available through the NMOP.	Non-applicable	The BCF listing for LMWHs specifies that "all MTFs must have at least one of the following products on the MTF formulary: ardeparin (Normiflo®); dalteparin (Fragmin®); danaparoid (Orgaran®); or enoxaparin (Lovenox®). MTFs will select the specific brand." The listing was amended to include tinzaparin as an option and to remove ardeparin, which is no longer available. The committee agreed that the class should be reviewed to assess the need for having the LMWHs available through the NMOP, the need for a prior authorization process at the NMOP/retail network to control inappropriately extended use, and the potential for contracting/incentive price agreements to reduce the unit cost of LMWH therapy. The VA is currently completing a LMWH clinical review, with a target date of Dec 00. The committee agreed that such an action could be done in conjunction with the VA.
Cande-sartan/ HCTZ tablets (Atacand HCT; AstraZeneca)	Approved 5 Sep 00 for treatment of hypertension	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added. The committee noted that there are currently no angiotensin receptor blockers (ARBs) on the BCF. While the clinical usefulness of the ARBs appears to be limited to patients who cannot tolerate ACE inhibitors due to cough, the comment was made that in light of increasing utilization it might be reasonable to review this class. The VA does not have a clinical review scheduled in the near future.

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Cole-sevelam HCl (Welchol; GelTex Pharma/ Sankyo Parke Davis)	Approved 30 May 00 as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia, administered alone or in combination with an HMG-CoA reductase inhibitor (non-absorbed agent)	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added. Colestipol, a bile acid sequestrant, is on the BCF. The committee asked the PEC to obtain more information to establish if a bile acid sequestrant continues to be required on the BCF and if colesevelam's apparent advantages of reduced constipation and fewer drug interactions make it a better choice for the BCF. The committee agreed that the PEC should wait until the Adult Treatment Panel III Guidelines are out and bring the issue back to the committee for consideration.
Beclo-methasone dipro-pionate HFA inhalation aerosol (QVar; 3M Pharma)	Approved 15 Sep 00 for the maintenance treatment of asthma as prophylactic therapy; and for asthma patients who require systemic corticosteroid administration, where adding QVar may reduce or eliminate the need for the systemic corticosteroids	Added	**NMOP Preferred Drug Program** No **Quantity Limits** **40-mcg strength:** 4 inhalers per 30 days, 12 inhalers per 90 days **80-mcg strength:** 2 inhalers per 30 days, 6 inhalers per 90 days. **Prior Authorization** No	Not added

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca)	Approved 8 Aug 00 for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age	Added	**NMOP Preferred Drug Program** No **Quantity Limits 0.25-mg strength:** 4 boxes of 30 per 30 days, 12 boxes of 30 per 90 days **0.5mg strength:** 2 boxes of 30 per 30 days, 6 boxes of 30 per 90 days **Prior Authorization** No	Not added
Unoprostone isopropyl ophthalmic solution, 0.15% (Rescula; Ciba Vision/ Novartis)	Approved 3 Aug 00 for lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Azelastine HCl ophthalmic solution, 0.05% (Optivar; ASTA Medica)	Approved 22 May 00 for treatment of itching of the eye associated with allergic conjunctivitis	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Levo-floxacin ophthalmic solution, 0.5%, (Quixin; Santen)	Approved 21 Aug 00 for the treatment of bacterial conjunctivitis	Added The committee noted that although there is little reason for prescriptions for the 7-day regimen of Quixin to be filled through the NMOP, other acute use antibiotics are available through the NMOP.	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Estradiol/ norethin-drone acetate tablets (Activella; Pharmacia & Upjohn)	Approved 11 Apr 00 for women with an intact uterus for the prevention of postmenopausal osteoporosis	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Atova-quone/ proguanil (Malarone; Glaxo Wellcome)	Approved 14 July 00 for the prevention and treatment of acute, uncomplicated Plasmodium falciparum malaria. Dosing recommendations in labeling for pediatric patients > 11 kg.	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added The committee noted that this drug has more application for readiness applications than for managed care. Special note was made of the pediatric indications for Malarone. LTC Greg Russie from the Joint Readiness Clinical Advisory Board commented that it is likely that facilities that need the agent for deployment purposes will have it, while active duty dependents traveling overseas will have access to the drug through the NMOP.

Generic name (Trade name; manufacturer)	**Indication, approval date**	**NMOP Formulary Status**	**NMOP or retail network formulary restrictions**	**BCF Status**
Lopinavir/ ritonavir solution (Kaletra; Abbott)	Approved 15 Sep 00 for the treatment of HIV-1 infection in adults and pediatric patients age six months and older	Added	**NMOP Preferred Drug Program** No **Quantity Limits** General rule applies **Prior Authorization** No	Not added
Eflornithine HCl 13.9% cream (Vaniqa; Bristol-Myers Squibb)	Approved 28 Jul 00 for the reduction of unwanted facial hair in women	Excluded Drugs intended for purely cosmetic purposes are not covered under the TRICARE benefit.	Non-applicable	Not added
Bexarotene gel (Targretin gel; Ligand)	Approved 29 Jun 00 for the topical treatment of cutaneous lesions in patients with early-stage (TNM Stage IA and IB) cutaneous T-cell lymphoma (CTCL) who have refractory or persistent disease after other therapies or who have not tolerated other therapies	Excluded It does not appear feasible to meet strict requirements for avoiding pregnancy (including limiting to a one month supply, monthly pregnancy tests, and frequent counseling) in a mail-order program. Oral bexarotene was excluded from the NMOP Formulary in Feb 00.	Non-applicable	Not added

APPENDIX B: ITEMS TO BE ADDRESSED AT THE NEXT MEETING

1. Report of the subcommittee to develop standard procedures for MTFs to request BCF changes and propose agenda items for the DoD P&T Committee and follow-up on placement of a form on the PEC website for MTF providers and other DoD personnel involved in the prescribing process to propose additions, deletions, or changes to the BCF. Subcommittee members include: MAJ George Jones (chair), MAJ Barbara Roach (PEC), MAJ Brett Kelly, CDR Matt Nutaitis, MAJ Mickey Bellemin, LTC Judith O'Connor.

2. NMOP preferred drug program standing report – CDR Mark Brouker (PEC)

3. NMOP prior authorization program standing report – MAJ Mickey Bellemin, Shana Trice (PEC)

4. Controlled distribution of alendronate (Fosamax) 40 mg (for Paget's Disease)

5. Controlled distribution of dofetilide (Tikosyn)

6. Controlled distribution of etanercept (Enbrel)

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MCCS-GPE **15 Nov 00**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The inaugural meeting of the DoD P&T Executive Council convened at 0800 hours on 15 November 2000, at Ft Sam Houston, TX. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. **MEMBERS PRESENT:**

CDR Terrance Egland, MC	P& T Committee Co-chair
COL Daniel D. Remund, MS	P& T Committee Co-chair
MAJ Brett Kelly, MS	Army
LTC Judith O'Connor, MC	Army
CDR Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL (select) John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs
LTC Greg Russie, BSC	Joint Readiness Clinical Advisory Board
LTC Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia

MEMBERS ABSENT:

COL Rosa Stith, MC	Army

OTHERS PRESENT:

COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LTC (P) William Davies, MC	DoD Pharmacy Program Director, TMA
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LCDR Fred Beale, MSC	Defense Supply Center Philadelphia
LCDR Mark Richerson, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
HM3 Cory Beckner	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Howard Altschwager	Deputy General Counsel, TMA
Shana Trice	DoD Pharmacoeconomic Center
Vincent Valinotti	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia

3. **IMPLICATIONS OF THE FY00 AND FY01 DEFENSE AUTHORIZATION ACTS** – COL Remund and LTC (P) Davies briefed the committee on implications of the FY00 and FY01 Defense Authorization Acts for the BCF. The BCF should be expanded to ensure uniform availability of cost-effective pharmaceuticals that will satisfy the primary care needs of the vast majority of patients served by MTF pharmacies. The DoD Pharmacoeconomic Center (PEC) will analyze drug usage data from MTF pharmacies, the NMOP and retail pharmacy networks to assist the committee in selecting additional pharmaceuticals for inclusion on the BCF at the next P&T meeting.

4. **NATIONAL PHARMACEUTICAL CONTRACTS**

A *Contract awards and renewals*

- The proton pump inhibitor (PPI) contract for omeprazole (Prilosec; Zeneca) was renewed. The price decreased from $1.40 to $1.10 per capsule.

- The FDA approved the marketing of the 0.8 mg dosage of cerivastatin (Baycol; Bayer). The 0.8 mg tablet is not being added to the statin contract, but is available at a DAPA price of $0.50 per tablet. According to package labeling, 0.8 mg/day of cerivastatin reduces LDL cholesterol by 42% and raises HDL cholesterol by 9% after 8 weeks of therapy. A 0.8 mg daily dose of cerivastatin costs $183 per year and provides approximately the same percent reduction in LDL-C as simvastatin 40 mg/day, which costs $361 per year.

- Joint VA/DoD single source contracts were awarded for acetaminophen, acyclovir, azathioprine, hydroxyurea, pentoxifylline, rifampin, sucralfate, and terazosin.

- Joint VA/DoD single source contracts were renewed for ranitidine, insulin, prazosin, and cimetidine.

- Prices and effective dates for contracts are available on the DSCP website.

B. *Financial impact of contracts* – Incomplete prime vendor data impaired the accuracy of previous estimates of the financial impact of national pharmaceutical contracts. The Defense Supply Center Philadelphia (DSCP) recently provided more complete prime vendor data to the PEC. Analysis of the more complete data revealed that MTFs spent approximately $1.03 billion on pharmaceuticals through the prime vendor system in FY 00. MTF cost avoidance from national pharmaceutical contracts was approximately $62.8 million in FY 00. A summary of MTF cost avoidance from national pharmaceutical contracts is provided in Appendix A. Market share and cost avoidance data associated with national pharmaceutical contracts are also available on the PEC website.

C. *Status of joint VA/DoD solicitation for non-sedating antihistamine contract* – Pharmaceutical companies have submitted multiple GAO protests to the solicitation. The PEC is working with the VA Pharmacy Benefit Management (PBM) Strategic Healthcare Group, the VA National Acquisition Center (NAC), and DSCP to resolve the protests.

D. *Status of contracting initiatives for oral contraceptives* – LCDR Beale reported that DSCP received no bids by the closing date of the solicitation for a joint VA/DoD single source contract for 35 mcg ethinyl estradiol (EE) / 1 mg norethindrone. DSCP plans to reissue the solicitation. DSCP also plans to issue solicitations for joint VA/DoD single source contracts for 35 mcg EE / 1 mg ethynodiol diacetate; EE 30/40/30 mcg / levonorgestrel 0.05/0.075/0.125 mcg; and 0.35 mg norethindrone.

E. *Returned goods contract* – LCDR Beale reported on DSCP's efforts to establish a returned goods contract.

F. *Potential future contract initiatives* – Potential candidates for future joint VA/DoD single source contracts include spironolactone, ticlopidine, isosorbide, diclofenac, ketoconazole cream, capsaicin cream, valproic acid, and hydrochlorothiazide.

5. **FLUOROQUINOLONES** – The committee considered safety, tolerability, efficacy and other pertinent factors and concluded that fluoroquinolones are not sufficiently interchangeable for a closed class contract. Fluoroquinolones differ significantly in adverse event profiles, spectrum of activity, and FDA-approved indications. The committee was also concerned that a closed class contract would preclude the use of new fluoroquinolones that may be approved by the FDA in the near future. The new fluoroquinolones may offer significant clinical advantages over existing agents.

   The committee selected levofloxacin for the BCF. The safety, tolerability and efficacy of levofloxacin are equivalent to or better than other fluoroquinolones. MTF fluoroquinolone usage has shifted away from ciprofloxacin in favor of levofloxacin over the past two years. Levofloxacin now accounts for nearly 70% of all fluoroquinolone prescriptions dispensed at

MTFs. The shift in market share was likely spurred by a blanket purchase agreement (BPA) that offered levofloxacin at a price of $2.00 per daily dose if levofloxacin attained a 60% market share at an MTF. Levofloxacin cost $2.50 per daily dose if the 60% market share was not achieved. A recent modification of the levofloxacin BPA lowers the market share requirement to 50%, but MTFs that do not meet the market share requirement will now pay the federal ceiling price of $3.25 per day for levofloxacin.

Some MTFs report that they are unable to obtain levofloxacin at the BPA price because purchases of ciprofloxacin for readiness requirements have artificially depressed the levofloxacin market share at their facilities. This problem is more prevalent at Air Force and Coast Guard pharmacies. The committee encouraged DSCP to modify the terms of the BPA so that MTFs can more easily obtain levofloxacin at the BPA price.

The fluoroquinolone class remains open on the BCF, so MTFs may have fluoroquinolones on their formulary in addition to levofloxacin. The committee is aware that ciprofloxacin is the only fluoroquinolone approved for the treatment of anthrax. The committee stressed that the selection of levofloxacin for the BCF has no bearing on the purchase of ciprofloxacin for readiness requirements.

6. **LEUTINIZING HORMONE RELEASING HORMONE (LHRH) AGONISTS** – The committee considered the PEC clinical review (available on the PEC website) and concluded that it is not possible to establish a closed class contract for a single agent to cover all nine clinical conditions that are treated with LHRH agonists. Seven of the clinical conditions affect only woman or children and two conditions affect only men. None of the four LHRH agonists is indicated for all the clinical conditions. The PEC estimates that 58% of MTF prescriptions for LHRH agonists are for prostate cancer and this usage is fairly evenly split between goserelin and leuprolide. Leuprolide accounts for nearly all the MTF usage for conditions other than prostate cancer.

   The committee concluded that goserelin and leuprolide are equivalent in regard to safety, tolerability, efficacy and other pertinent factors in the treatment of prostate cancer, so it is theoretically possible to establish a closed class contract for the specific indication of prostate cancer. The committee decided not to seek a closed class contract at this time. Since the VA already has a closed class contract for goserelin for treatment of prostate cancer, a joint VA/DoD contract should not be pursued until the VA is ready to rebid the contract. If DoD were to establish its own closed class contract now, it would likely hinder the ability to solicit for a joint VA/DoD contract in the future. The committee also has concerns about the potential complexity of administering a closed class contract for a specific indication within the military health system.

   The committee was informed of a recent voluntary price reduction for leuprolide and an offer of a blanket purchase agreement (BPA) for goserelin (see Appendix B for price information and BPA terms). The BPA prices for goserelin are equal to the VA national contract prices and are substantially lower than the prices for equivalent doses of leuprolide for prostate cancer. The committee advised DSCP to accept the BPA for goserelin. The committee asked DSCP and the PEC to initiate an education/marketing campaign to ensure that goserelin

achieves at least an 80% overall share of the MTF prescriptions for LHRH agonists for prostate cancer as required by the BPA. The PEC will use the Uniformed Services Prescription Database (USPD) to track the market shares for LHRH agonists for prostate cancer.

7. **NASAL INHALED CORTICOSTEROIDS** – The committee reviewed a draft of the VA clinical review and MTF usage and cost data for intranasal corticosteroids. The committee made the following observations and conclusions:

   - Nasal corticosteroids are widely used as first line agents in treating nasal symptoms of seasonal and perennial allergic rhinitis.

   - Nasal corticosteroids do not differ significantly in their safety profiles. All nasal corticosteroids carry the same warning regarding potential suppression of growth in children.

   - Patients generally tolerate the aqueous formulations better than the non-aqueous formulations.

   - All nasal corticosteroids can be considered equally effective for seasonal and perennial allergic rhinitis when used in equipotent doses. Agents that are normally dosed once or twice daily are commonly classified as "high potency" agents. These agents are budesonide 32mcg/spray, fluticasone 50mcg/spray, triamcinolone 55mcg/spray, mometasone 50mcg/spray, and beclomethasone 84mcg/spray.

   - Annual MTF usage of nasal corticosteroids has remained relatively constant, but annual expenditures have nearly doubled over the past three years due to large price increases for some of the agents. Significant shifts in market share have occurred over the past two years—probably in response to the large price increases. Two years ago, beclomethasone inhalers accounted for 80% of all nasal corticosteroid prescriptions filled at MTFs—now they account for only 20% of the prescriptions. Fluticasone 50mcg/spray (the only nasal corticosteroid inhaler currently on the BCF) and mometasone 50mcg/spray now account for 60% and 20% respectively of all nasal steroid prescriptions filled at MTF pharmacies.

   The committee agreed that the nasal corticosteroid inhaler class can be divided into two categories: aqueous and non-aqueous formulations. The aqueous formulations can be further subdivided into high potency and low potency categories. The committee concluded that the BCF must contain, at a minimum, a high potency aqueous nasal corticosteroid. The committee agreed that a closed class contract could be established for a high potency aqueous corticosteroid inhaler. The committee recommended that this should be a joint VA/DoD contract if the requirements of the two agencies are conducive to such a contract. The committee also supports a closed class contract for a non-aqueous corticosteroid inhaler if those involved in the contracting process conclude that it would be beneficial to seek such a contract.

8. **ORAL INHALED CORTICOSTEROIDS** – The committee considered the PEC clinical review (available on the PEC website) and made the following observations and conclusions.

- High potency agents (budesonide and fluticasone) are not interchangeable with low potency agents (beclomethasone, triamcinolone, and flunisolide). Patients with moderate to severe asthma often prefer a high potency agent because they can obtain the necessary dosage with fewer puffs per day than with low potency agents.

- Budesonide and fluticasone are not sufficiently interchangeable because fluticasone is available as a metered dose inhaler (MDI) and a dry powder inhaler (DPI) and budesonide is available only as a DPI. Some patients do not like using the breath-actuated DPI because it lacks the tactile feedback associated with an MDI that uses a propellant to deliver the drug. Breath actuation may be particularly difficult for pediatric patients. Patients who need to use a spacer with a face mask cannot use a budesonide DPI.

- The bitter taste of flunisolide limits its interchangeability with other low potency agents.

- The triamcinolone inhaler comes with a built-in spacer. While this ensures the use of a spacer, the spacer is relatively low volume and does not work well with a face mask.

The committee concluded that oral corticosteroid inhalers are not sufficiently interchangeable for a closed class contract for the overall class or the high potency or low potency categories. The committee discussed the possibility of adding a high potency oral corticosteroid inhaler to the BCF, but concluded that the issue should be addressed in the process of selecting additional agents for the BCF at the next P&T meeting.

9. **POTENTIAL ADDITION OF A THIAZOLIDINEDIONE ("GLITAZONE") TO THE BCF**
The thiazolidinediones currently on the market are rosiglitazone and pioglitazone. Troglitazone was withdrawn in March 2000 due to cases of hepatotoxicity and liver failure, some fatal. The committee agreed that post marketing surveillance has not yet proven conclusively that rosiglitazone and pioglitazone are free from similar safety problems. The committee also discussed the side effect of edema and weight gain known to occur with the glitazones and the related contraindication in patients with New York Heart Association Class III and IV heart failure. Although the glitazones are approved for monotherapy, clinical practice guidelines (including the DoD/VA Clinical Practice Guideline for diabetes) and expert opinion currently support use of glitazones only as add-on medications following sulfonylureas, metformin, and possibly other antidiabetic agents. The committee concluded that a thiazolidinedione should not be added to the BCF at this time.

10. **SELECTION OF A TRIPTAN FOR THE BCF (EVALUATION OF BPA PRICE QUOTES)**

The committee considered the PEC class review (available on the PEC website) of oral 5-HT_1 receptor agonists (triptans) and concluded the following:

- There are no clinically significant differences in the overall safety profiles of the individual triptans.

- Patients probably tolerate naratriptan better than the other triptans (the incidence of adverse events experienced by patients in phase III trials was similar to placebo). No significant differences in tolerability can be discerned between the other agents

- The efficacy of triptans can be measured by how fast they relieve headaches, to what degree they relieve headaches, and how frequently the headaches reoccur. Some studies suggest that rizatriptan may be slightly more efficacious than sumatriptan and zolmitriptan, but the available evidence is insufficient to conclude that there is any clinically significant difference in efficacy between rizatriptan, sumatriptan and zolmitriptan. Naratriptan should not be considered a first line agent because of its slower onset of action.

    - Head-to-head trials suggest that rizatriptan may provide earlier and/or more complete headache relief than either sumatriptan or zolmitriptan.

    - Two published meta-analyses of several studies found no significant differences in the "number needed to treat (NNT)" for sumatriptan, rizatriptan, and zolmitriptan. The NNT for naratriptan was significantly higher.

    - The PEC tried to compare the data from various clinical trials that measured efficacy in terms of the percentage of patients who obtained headache relief at two hours after the first dose of a triptan. In an effort to control for factors that may have varied between the trials, the PEC calculated the incremental efficacy of the triptan compared to placebo by subtracting the percentage of patients who obtained relief on placebo from the percentage of people who obtained relief on the triptan. This analysis showed a slightly higher incremental efficacy for rizatriptan. A formal statistical analysis was not performed, but it is likely that the difference between rizatriptan and the other triptans was not statistically significant.

The committee then considered the weighted average cost per prescribed dose for each triptan, which was derived from a frequency distribution of the prescribed doses and the price per tablet for each strength of each triptan. The frequency distributions of prescribed doses were obtained from the USPD. The price per tablet reflected the prices offered by pharmaceutical companies in response to a Blanket Purchase Agreement (BPA) request for price quotes issued by DSCP. The DAPA price was used if a company did not submit a price quote.

The committee concluded that sumatriptan offered the greatest value to DoD. Sumatriptan is similar in safety, tolerability and efficacy to rizatriptan and zolmitriptan. The price quote of $6.95 for sumatriptan 50 mg and 100 mg tablets reflects a 5% price reduction from the existing DAPA prices. Given the fact the sumatriptan accounts for 93% of the triptan usage at MTFs, acceptance of the sumatriptan price quote will yield the greatest cost avoidance for DoD.

The committee voted to add sumatriptan to the BCF. The triptan class remains open on the BCF. The committee emphasized that the addition of sumatriptan to the BCF is not intended to cause MTFs to delete other triptans from their formularies or to switch patients who are already using other triptans to sumatriptan.

11. **UPDATE AND REVISION OF THE ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM** – Total MTF expenditures and reimbursements in FY 00 for drugs covered by the AMP Program are given in the table below. Total expenditures were just slightly more than the $48.8 million that was programmed for pharmacy in the FY 00 AMP program.

	MTF Expenditures	AMP Reimbursement
All AMP drugs other than COX-2 inhibitors	$43,377,976	$43,377,976
COX-2 inhibitors*	$13,862,741	$6,931,370
Total	**$57,240,717**	**$50,309,346**

* reimbursed at 50%

Only $50.7 million in AMP funds are projected to be available for pharmacy in FY 01, which will be insufficient to cover the drugs currently included in the AMP program. During the last 3 months of FY 00, MTFs spent an average of $4 million per month on AMP drugs other than COX-2 inhibitors. It would be reasonable to project that expenditures for AMP drugs other than COX-2 inhibitors could easily exceed the $50.7 million in AMP funds programmed for pharmacy in FY 01. Expenditures for COX-2 inhibitors averaged nearly $2 million per month during the last 3 months of FY 00. Even if expenditures for COX-2 inhibitors in FY 01 leveled off at the expenditure rate observed in the last three months of FY 00, pharmacy would still require $12 million above the projected AMP program to reimburse MTFs for COX-2 inhibitors in FY 01. The committee concluded that COX-2 inhibitors should be removed from coverage under the AMP program because funds available to pharmacy are insufficient to support their reimbursement under the AMP program.

12. **CONSIDERATION OF COMBINATION DRUGS FOR THE BCF** – The committee discussed pros and cons of having combination drugs on the BCF. Combination drugs might offer the advantages of greater convenience and improved compliance for patients. They also could possibly reduce workload for pharmacies if a prescription for one combination product actually replaces two prescriptions for individual products. Combination products pose the disadvantages of fixed dosages that preclude adjustment in the dosage of the component drugs and the potential for unnecessary exposure to drugs if a combination product is used when a single drug would have sufficed.

The committee considered Glucovance, a newly-approved combination of metformin and glyburide. Even though Glucovance is priced slightly lower than the combined cost of the individual drugs, the committee decided not to add Glucovance to the BCF. Generic versions of metformin are expected to be available in less than a year, so the cost advantage offered by Glucovance will likely be a short-term phenomenon. The committee expects that cost of

generic versions of the individual drugs will likely be significantly less than the cost of Glucovance.

The committee considered Combivent inhaler, a combination of ipratropium and albuterol. While patients may find Combivent more convenient to use than separate inhalers, there is no conclusive evidence that patient compliance is improved significantly. Combivent costs slightly more than individual ipratropium and albuterol inhalers. The higher cost might be offset by reduced usage of albuterol inhalers, but conclusive data are not available. The committee decided not to add Combivent to the BCF.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

Appendix A: Estimated Cost Avoidance in DoD MTFs Due to National Pharmaceutical Contracts, Fiscal Year 2000

Total FY00 prime vendor purchases in DoD MTFs were $1,024,591,068. The total cost avoidance of $62,804,712 for FY00 was equal to 6.13% of the total FY00 prime vendor purchases.

Drug/Drug Class	Cost Avoidance
Statins	$22,340,377
PPIs	$19,297,055
Lisinopril	$10,072,755
Diltiazem	$6,967,368
Ranitidine	$1,862,449
Albuterol	$923,293
Timolol Gel	$540,882
Verapamil	$413,898
Cimetidine	$292,913
Captopril	$135,558
Nortriptyline	$83,643
Amoxicillin	$60,492
Timolol Drops	$31,473
Fluocinonide	$14,749
Prazosin	$14,153
Amantadine	$5,796
Insulin	($252,142)
TOTAL FY00	**$62,804,712**

Appendix B: Cost Considerations – Goserelin and Leuprolide Depot for Prostate Cancer

MAGNITUDE OF DOD EXPENDITURE: DoD can expect to spend approximately $5 million for 17,500 LHRH agonist prescriptions in FY01. Approximately 58% of these, or 10,000 prescriptions, will be for strengths used for prostate cancer. These 10,000 prescriptions are currently split almost evenly between goserelin and leuprolide. Over 97% of the remaining LHRH agonist prescriptions are for leuprolide.

DOD PRICING FOR GOSERELIN AND LEUPROLIDE DEPOT FORMULATIONS

	Goserelin				**Leuprolide**		
	Dosage Form	**Nov 00 DAPA price**	**BPA Price*** (equals VA contract price)		**Dosage Form**	**Oct 00 DAPA Price**	**Nov 00 DAPA Price** (resulting from voluntary price reduction)
1-month depot	3.6 mg implant	$213.80	$140.67		7.5 mg depot	$257.00	$227.21
3-month depot	10.8 mg implant	$611.62	$418.70		22.5 mg depot	$770.99	$681.63
4-month depot	Not available				30 mg depot	$976.58	$908.84

*The BPA for goserelin provides for a direct, immediate modification of the prime vendor price, not a rebate. The requirement is that goserelin achieve >80% market share of the prostate cancer market within 9 months (by August 2001).

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE 17 Aug 2000

MEMORANDUM FOR: Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 17 August 2000, at the Uniformed Services School of the Health Science, Bethesda, MD.

2. MEMBERS PRESENT:

CDR Terrance Egland, MC	Co-chair
COL Daniel D. Remund, MS	Co-chair
COL Mike Heath, MS	Army
LTC Judith O'Connor, MC	Army
CDR Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL (select) John R. Downs, MC	Air Force
LTC Deborah Bostock	Air Force (alternate)
MAJ George Jones, BSC	Air Force
LCDR Pam Stewart-Kuhn	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services

MEMBERS ABSENT:

COL Rosa Stith, MC	Army

Joint Readiness Clinical Advisory Board representative
Department of Veterans Affairs representative

OTHERS PRESENT

LTC (P) William Davies	DoD Pharmacy Program Director, Tricare Management Activity (TMA)
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Brett Kelly, MS	TRICARE Lead Agent Office (Region 1)
Howard Altschwager	Deputy General Counsel, TMA
David Chicoine	Uniformed Services Family Health Plan
Linda Magazu	Defense Supply Center Philadelphia
Mark Petruzzi	Merck-Medco
Elizabeth Scaturro	Merck-Medco
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

3. ADMINISTRATIVE ISSUES

   The minutes from the last meeting were accepted as written. COL Mike Heath replaced Danielle Doyle as the Army pharmacy representative.

4. REVIEW OF INTERIM DECISIONS – The co-chairs made an interim decision to institute the same quantity limits in the National Mail Order Pharmacy (NMOP) program and the retail network for ondansetron oral dissolving tablets (Zofran ODT) as those currently in place for ondansetron tablets (Zofran). The committee agreed with the interim decision.

5. UPDATE ON THE ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM – COL Remund presented military treatment facility (MTF) prime vendor expenditure data through May 00 for drugs covered under the AMP program. Accurate prediction of the total AMP expenditures for FY 00 is impossible because prime vendor data are missing for numerous military treatment facilities (MTFs). The "best guess" is that total MTF expenditures for AMP drugs will be around $47 million in FY 00, which will use up all the AMP funds available for pharmacy. The committee decided to make no changes in the drugs covered by the AMP program until we are more certain about expenditures for AMP drugs in FY 00 and we know how much AMP funding will be available for pharmacy for FY 01.

6. UPDATE ON BCF ADDITIONS RESULTING FROM PROGRAM BUDGET DECISION (PBD) 041 – COL Remund presented prescription data from the Uniformed Services Prescription Database (USPD) for the drugs added to the Basic Core Formulary (BCF) in Jan 00 as a result of PBD 041. A marked increase in the number of prescriptions filled for these drugs indicates that MTFs have generally complied with BCF policy by adding these drugs to their formularies.

7. SELECTION OF AN ADDITIONAL ACE INHIBITOR FOR THE BCF

The primary purpose of adding another long-acting ACE inhibitor to the BCF is to ensure uniform availability at all MTFs of an additional agent within a class of drugs that is known to provide significant clinical benefits at a reasonable cost. The ACE inhibitor clinical review prepared by the PEC will be posted on the PEC website. The committee first considered the relative safety, tolerability, efficacy, and other factors pertaining to ACE inhibitors and agreed that:

- Fosinopril may offer a slight safety/convenience advantage in patients with renal or hepatic failure due to its lack of dose adjustment requirements.
- There is insufficient evidence to conclude that ACE inhibitors differ significantly in their propensity to cause cough.
- All long-acting ACE inhibitors appear to be similar in efficacy for hypertension.
- Benazepril, enalapril and ramipril have the most evidence of a beneficial effect on renal disease/diabetic nephropathy.
- Enalapril and ramipril have the most extensive evidence of reduction in morbidity and mortality in patients with congestive heart failure (CHF), post-myocardial infarction (MI), or asymptomatic left ventricular (LV) dysfunction. Trandolapril has evidence of reduction in morbidity and mortality in a subset of these patients (LV dysfunction post MI). Fosinopril, quinapril, and perindopril have evidence of a beneficial effect on signs and symptoms of CHF and on disease progression, but lack mortality data. Moexipril and benazepril have little or no evidence supporting use in these patient populations.
- Ramipril appears to be the only ACE inhibitor with evidence of a reduction in the risk of stroke in patients at high cardiovascular risk.

The committee then considered the weighted average daily cost per patient for each ACE inhibitor, which was derived from the frequency distribution of prescribed daily doses and the price per tablet for each strength of each ACE inhibitor. The frequency distributions of prescribed daily doses were obtained from the USPD. The price per tablet reflected the prices offered by pharmaceutical companies in response to a Blanket Purchase Agreement (BPA) request for price quotes issued by Defense Supply Center Philadelphia. The DAPA price was used if a company did not submit a price quote.

Ramipril had the second lowest weighted average daily cost per patient, which was only $0.008 more than the lowest cost ACE inhibitor (a difference of $2.92 per patient per year). The committee concluded that ramipril offered the greatest value to DoD because its extensive evidence of proven clinical benefits for a variety of conditions outweighed its slightly higher cost. The committee decided (by a vote of 8 to 1) to add ramipril to the BCF.

The ACE inhibitor class remains open on the BCF. The committee emphasized that the addition of ramipril to the BCF is not intended to cause MTFs to delete other ACE inhibitors from their formularies or to switch patients who are already using other ACE inhibitors to ramipril.

8. STATUS OF ORTHO NOVUM 7/7/7 ON THE BCF – Ethinyl estradiol 35 mcg/norethindrone 0.5/0.75/1 mg (Ortho-Novum 7/7/7) is one of two oral contraceptive products still available

through the DSCP Centrally Managed Inventory Program (the depot). The price of Ortho-Novum 7/7/7 through the depot is approximately $5.56 per cycle, including surcharge, compared to $15.78 per cycle through the prime vendor program (DAPA price as of May 00). The Ortho-Novum 7/7/7 packages stocked in the depot are clinic packs, which cannot be included under the prime vendor program. About 64% of the estimated 274,000 cycles of Ortho-Novum 7/7/7 purchased by MTFs from Apr 99 to Mar 00 were obtained from the depot. The DSCP product manager expects that the product will continue to be available through the depot until at least 2002. The committee agreed that Ortho-Novum 7/7/7 should remain on the BCF, but strongly encouraged MTFs to order the product through the depot.

9. STATUS OF OXYCODONE/ACETAMINOPHEN ON THE BCF – The BCF currently requires MTFs to have both the 5/325 and 5/500 mg strengths of oxycodone/acetaminophen on their formularies. MTF pharmacists contend that both strength combinations are not needed at all MTFs. The committee agreed to change the BCF to state: "oxycodone/acetaminophen 5/325 mg *and/or* 5/500mg." MTFs may decide to have one or both combinations on their formularies.

10. PROCEDURE FOR REQUESTING BCF CHANGES – The committee appointed a subcommittee to develop standard procedures for MTFs to request changes to the BCF and to propose agenda items for the DoD P&T Committee. The subcommittee will present its recommendations at the next meeting. Subcommittee members include: MAJ George Jones (chair), MAJ Barbara Roach (PEC), MAJ Brett Kelly, CDR Matt Nutaitis, MAJ Mickey Bellemin, LTC Judith O'Connor.

11. NATIONAL PHARMACEUTICAL CONTRACTS, BLANKET PURCHASE AGREEMENTS, AND INCENTIVE PRICE AGREEMENTS

    A. *Contracts Awarded Since Last Meeting* – LTC De Groff reported that a joint DoD/VA single source contract for terazosin tablets and capsules was awarded with a start date of 5 Sep 00. Contract prices are approximately 70% less than the pre-contract prices. DoD MTFs purchased at least $6.1 million of terazosin tablets and capsules through the prime vendor program during FY99.

    B. *Financial Impact of Contracts* – COL Remund reported cumulative cost avoidance for national pharmaceutical contracts based on prime vendor data through May 00. Cost avoidance information is maintained on the PEC website. Accurate calculation of cost avoidance is impossible because prime vendor data are missing for numerous MTFs. The "best guess" is that cost avoidance from national pharmaceutical contracts will total approximately $52 million for MTFs in FY 00. To put this in context, total expenditures at MTF pharmacies in FY99 were $878 million.

    COL Remund also reported that efforts by the PEC and DSCP to monitor the financial impact of national pharmaceutical contracts have yielded additional benefits. SFC (P) Tom Bolinger, NCOIC at the PEC, discovered that a prime vendor had charged an MTF the wrong price for three drugs. Correction of the pricing errors resulted in a $236,500 credit for that MTF.

C. *Potential contract for Extended Release Morphine* – The committee considered the possibility of competing MS Contin, "A-rated" generic equivalents to MS Contin, Oramorph SR, and Kadian against each other for a closed class contract. MTF providers contend that MS Contin has a longer duration of action than Oramorph SR, and two published studies support that contention. Kadian is dosed once daily, while the other products typically require multiple daily doses. The committee concluded that these drugs are not sufficiently interchangeable for a closed class contract.

D. *Potential Contracts for Oral Contraceptives* – The committee reiterated that single source contracts should be sought for each of the following oral contraceptive agents:

1) ethinyl estradiol (EE) 35 mcg / norethindrone 1 mg
2) EE 35 mcg / ethynodiol diacetate 1 mg
3) EE 30/40/30 mcg / levonorgestrel 0.05/0.075/0.125 mcg
4) norethindrone 0.35 mcg

E. *Returned Goods Contract* – Linda Magazu updated the committee on the status of the returned goods contract.

F. *Generic 2000 and 2000B packages (VA lead)* – LTC De Groff reported on the progress of joint DoD/VA single source contracts for multi-source drugs included in the Generic 2000 and 2000B packages. The Generic 2000 package includes acyclovir, azathioprine, etodolac, furosemide, glipizide, hydroxyurea, pentoxifylline, rifampin, selegiline, and sucralfate. The Generic 2000B package includes albuterol immediate release, amitriptyline, bupropion, buspirone, carbidopa/levodopa sustained action, carisoprodol, capsicum, diclofenac, hydrochlorothiazide, imipramine, isosorbide, ketoconazole cream, meclizine, methocarbamol, prednisone, sotalol, spironolactone 50- and 100-mg, sulindac, ticlopidine, verapamil immediate release, and valproic acid. An extensive 2000C package may be developed as drugs come off VA contracts in the next six months.

The committee reiterated that contracts for single sources of "A-rated" multi-source products do not normally require prior review by the DoD P&T Committee.

G. *General Accounting Office (GAO) Report – Review of Drug Classes for Contracting Potential* – The committee reviewed the GAO recommendations regarding drug classes that may be suitable for joint DoD/VA committed use contracts. The committee supports developing joint DoD/VA contracts whenever possible. The committee came to the following conclusions regarding the potential for contracts in seven drug classes as described below:

1) *$5HT_1$ receptor agonists for migraine ("triptans")* – The committee concluded that the oral triptans are not sufficiently interchangeable for a closed class contract because of variability in patient response to these agents. The committee decided that an oral triptan should be selected for the BCF in an open class to ensure uniform availability of one oral triptan while allowing MTFs to have additional oral triptans on their formularies. The PEC will do a clinical review and DSCP will obtain pricing

information by issuing a BPA request for price quotes to companies that market oral triptans. The committee is hopeful that its evaluation of the clinical and pricing information will lead to the selection of an oral triptan for the BCF at the next meeting.

2) *Thiazolidinediones ("glitazones")* – This drug class cannot be closed because the class is too new to accurately assess the interchangeability of the drugs. The PEC will do a clinical review to assess the need for adding one of these agents to the BCF. If an agent should be added to the BCF, the committee will likely advise DSCP to issue a BPA request for price quote.

3) *Oral inhaled corticosteroids* – The PEC will do a clinical review to assess the interchangeability of these agents for a closed class contract. Members commented that separate contracts might be needed for low-potency and high-potency agents.

4) *Nasal inhaled corticosteroids* – The PEC will do a clinical review to assess the interchangeability of these agents for a closed class contract.

5) *Fluoroquinolones* – The committee discussed a number of factors that could complicate contracting efforts in this drug class, including readiness requirements for ciprofloxacin (approved for anthrax) and regional variations in antibiotic resistance. The committee decided not to rule out the possibility of a closed class contract until the PEC completes a clinical review.

6) *Leutinizing hormone releasing hormones (LHRHs; leuprolide (Lupron) and goserelin (Zoladex))* – The VA has a closed class contract for goserelin (Zoladex) for prostate cancer, but a closed class contract may not be appropriate for DoD because these drugs are less interchangeable in a patient population that includes more women and children. Lupron is indicated for prostate cancer, endometriosis, uterine fibroids and precocious puberty. Zoladex is indicated for prostate cancer, endometriosis and breast cancer. The PEC will do a clinical review to assess the interchangeability of these agents for a closed class contract.

7) *Non-sedating antihistamines* – LTC De Groff reported that the market share requirements in the current incentive price agreements for the non-sedating antihistamines are difficult for MTFs to achieve. The committee concluded that the incentive price agreements probably would not yield substantial cost savings for MTFs. In light of the large increase in MHS expenditures for these agents, the committee reconsidered the possibility of a closed class contract for a non-sedating antihistamine. The committee decided that its previous objections to a closed class contract for a non-sedating antihistamine would be obviated under the following conditions:

    - Loratadine and fexofenadine are classified as non-sedating antihistamines and cetirizine is classified as a low-sedating antihistamine. Loratadine and fexofenadine are the only two drugs that compete for the contract.

- The contracted drug is the only non-sedating antihistamine on the BCF. The non-sedating antihistamine class would be closed on the BCF, so the contracted drug would be the only non-sedating antihistamine permitted on MTF formularies.
- The contract does not affect the current status or future status of loratadine or fexofenadine in regard to the NMOP formulary.
- The contract does not affect the current status or future status of cetirizine in regard to the BCF, MTF formularies, or NMOP formulary (cetirizine is not a non-sedating antihistamine).
- The contract does NOT require DoD beneficiaries who are currently taking the non-contracted drug to switch to the contracted drug.

The committee recommended that a joint DoD/VA closed class contract should be pursued if the VA is willing to amend its contract solicitation to include the DoD requirements.

12. AVAILABILITY OF INFORMATION ON INCENTIVE PRICE AGREEMENTS AND NATIONAL PHARMACEUTICAL CONTRACTS – MAJ Cheryl Filby (DSCP) reminded the committee that the DSCP website contains information on all national contracts and a list of all incentive agreements that have come through DSCP for review. Copies of the incentive agreements are available from DSCP. She also noted that MTFs were encouraged to submit incentive price agreements to DSCP for review by DSCP legal staff and posting on the DSCP website in order to expand availability to other MTFs. In addition, the website contains a tool that may assist MTFs in verifying that they are complying with (and realizing the cost avoidance associated with) all the national contracts.

13. IMPLEMENTATION OF FY00 NATIONAL DEFENSE AUTHORIZATION ACT – LTC Davies briefed the committee on the ongoing efforts to implement the provisions of the FY00 National Defense Authorization Act pertaining to the Uniform Formulary and the DoD P&T Committee.

14. BCF AND NMOP FORMULARY ISSUES

A. The following recently approved drugs were added to the NMOP formulary. None of these drugs were added to the BCF.

1. *Triamcinolone acetonide nasal spray (Tri-Nasal; Muro Pharma)*, approved 4 Feb 00 for treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 12 years and older. Tri-Nasal will have a quantity limit of 6 bottles (45 gm) per 90 days in the NMOP and 2 bottles (15 gm) per 30 days in the retail network, which is consistent with the established quantity limits for other nasal corticosteroids.

2. *Zonisamide capsules (Zonegran; Elan)*, approved 31 Mar 00 for adjunctive treatment of partial seizures in adults 16 years and older with epilepsy.

3. *Meloxicam tablets (Mobic; Boehringer-Ingelheim/Abbott)*, approved 13 Apr 00 for relief of the signs and symptoms of osteoarthritis. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that is preferential but not completely selective for

cyclooxygenase-2 (COX-2). If COX enzyme selectivity is conceptualized as a spectrum, meloxicam, like nabumetone and etodolac, tends to bind more to COX-2 than cyclooxygenase-1 (COX-1), while drugs such as naproxen tend to bind more to COX-1 than COX-2. Unlike celecoxib and rofecoxib, meloxicam retains some activity at COX-1 receptors. Bill Hudson noted that Humana had opted to require prior authorization of meloxicam on the same terms as rofecoxib for its commercial (non-DoD) clients. The committee noted that managed care support contractors (MCSCs) can not currently impose prior authorizations for DoD beneficiaries beyond those approved by the DoD P&T Committee (see paragraph 16 below). The committee decided that meloxicam will be identified as a non-preferred drug (like other brand name NSAIDs) on the NMOP formulary.

4. *Pemirolast potassium ophthalmic solution (Alamast; Santen),* approved 24 Sept 99 for prevention of itching of the eye due to allergic conjunctivitis.

5. *Testosterone 1% gel (Androgel; Unimed Pharma),* approved 28 Feb 00 for primary hypogonadism secondary to testicular failure and hypogonadotropic hypogonadism secondary to gonadotropin deficiency.

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B. *Linezolid injection, tablets, and oral suspension (Zyvox; Pharmacia & Upjohn)* were excluded from the NMOP and were not added to the BCF. Linezolid was approved 24 Apr 00 for nosocomial and community acquired pneumonia and complicated/uncomplicated skin/skin structure infections caused by susceptible organisms, primarily aerobic gram-positive organisms, including *Enterococcus faecium* (vancomycin-resistant only), *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pneumoniae* (penicillin sensitive strains only), *Streptococcus galactiae*, and *Streptococcus pyogenes*. Because of the potential that bacterial resistance will develop if this drug is used indiscriminately, as well as the need for dispensing the drug on a more timely basis than is possible in a mail order program, the committee excluded linezolid from the NMOP formulary.

The committee discussed the possibility of instituting a prior authorization program in the retail network to ensure that linezolid is used only when truly indicated, thus minimizing the potential for development of bacterial resistance. The committee decided not to establish a prior authorization process because a delay in therapy due to the prior authorization process would pose a greater threat than the inappropriate use that might occur in the absence of a prior authorization process. The committee requested that the MCSCs monitor usage of linezolid in their systems and report back to the committee at the next meeting.

C. *Fluoxetine (Sarafem; Lilly*) – Sarafem is supplied with special packaging/labeling for Premenstrual Dysphoric Disorder (PMDD). The committee added Sarafem to the NMOP formulary. The committee decided that the BCF listing for fluoxetine should specify that MTFs are not required to have the Sarafem brand of fluoxetine on their formularies because:

- There are no chemical or formulation differences between Sarafem and Prozac. Prozac is on the BCF.
- While Sarafem and Prozac may be the same price now, a generic form of fluoxetine may be available as soon as 2001 and will probably be much less expensive than Prozac. The generic form will probably not be substitutable for Sarafem.
- The committee is skeptical that the specialized labeling for Sarafem offers any significant incremental value over the Prozac brand of fluoxetine.

15. NON-PREFERRED/PREFERRED DRUG PAIRS IN THE NMOP – CDR Mark Brouker reported the switch rates and estimated cost avoidance for the preferred drug program in the NMOP (see Appendix C). The NMOP preferred drug program yields approximately $1.8 million in annual cost avoidance for DoD.

    The committee removed cilostazol (Pletal) from the list of non-preferred drugs due to a low switch rate (see Appendix A). No report was made on the herpes antivirals, since the new strategy of calling only on prescriptions for valacyclovir and famciclovir written for chronic use (> 30-day supply) was not implemented until 1 Jul 00.

    The committee asked the PEC to instruct Merck-Medco to remove enalapril (Vasotec) from the list of non-preferred drugs as soon as generic enalapril is available at a price that is competitive with other ACE inhibitors.

16. FORMULARY CONTROLS IN THE RETAIL PHARMACY NETWORK – LTC Bill Davies and Howard Altschwager informed the committee that clarifications have been issued to the MCSCs concerning formulary controls in the retail pharmacy networks.

- The NMOP formulary does not apply to the retail pharmacy network.
- The federal regulations that implement the law governing TRICARE currently allow prior authorizations to be applied in the retail pharmacy networks only for clinical considerations (appropriateness of therapy). Terbinafine, itraconazole, sildenafil, and etanercept will continue to be subject to prior authorization in the retail network. The prior authorization for COX-2 inhibitors will be withdrawn in the retail pharmacy networks because it is based primarily on cost-effectiveness considerations rather than clinical appropriateness. The PEC will make all required changes to its website. ~~MCSCs can not currently impose prior authorizations beyond those approved by the DoD P&T committee.~~ *(This sentence was deleted as a correction to the minutes at the Nov 00 meeting of the DoD P&T Committee.)*
- Quantity limits continue to apply both to the NMOP and the retail pharmacy network.

- Active duty personnel may fill prescriptions at retail network pharmacies—including prescriptions for controlled substances.

- DoD closed class pharmaceutical contracts (i.e. contracts for statins and proton pump inhibitors) do not apply to the retail network pharmacies. Closed class contracts that apply only to MTF pharmacies and the NMOP cannot serve as the basis for denying prescriptions in the retail pharmacy networks.

17. PRIOR AUTHORIZATIONS

A. *Cost analysis of NMOP prior authorizations* – Shana Trice (PEC) presented the subcommittee's extensive cost analysis of prior authorizations (PAs) in the NMOP. Subcommittee members included MAJ Mickey Bellemin (DPSC), MAJ Brett Kelly (TRICARE Region 1 Lead Agent Office), Shana Trice (PEC), and Dave Beshara (Merck-Medco).

For each drug, the costs that would be incurred for 1000 new prescriptions submitted to the NMOP that are subject to the PA process were compared to the costs that would be incurred if the prescriptions were not subject to the PA process. The analysis takes into account the cost of drug therapy, the charge from Merck-Medco for performing the PA, the estimated number of refills associated with each new prescription and the estimated cost of alternative therapy for prescriptions not filled as a result of the PA process. The analysis does not quantify the "sentinel effect" of PAs (i.e., the possibility that providers prescribe the drug less frequently because they know the drug is subject to prior authorization).

The analysis showed that total costs for each drug would be higher without PA than they are with PA. The cost avoidance resulting from the PA process is shown in the following table:

Drug	Cost avoidance per new Rx submitted
Etanercept (Enbrel)	$327.20
Sildenafil (Viagra)	$13.60
COX-2 inhibitors	$11.66

B. *COX-2 inhibitors* – As addressed previously, the clarification of TRICARE policy caused discontinuation of the COX-2 inhibitor PA in the retail pharmacy networks. The committee decided to continue the PA for COX-2 inhibitors in the NMOP because TRICARE policy allows prior authorizations to be based on cost-effectiveness considerations in the NMOP and because the cost analysis showed that prior authorization yielded cost avoidance in the NMOP. The committee is also concerned that usage of COX-2 inhibitors would increase even more rapidly if they were not subject to the PA process. Much of the incremental COX-2 inhibitor usage would occur among patients who are at relatively low risk for gastrointestinal problems and therefore would offer negligible incremental benefit compared to using the much less expensive generic NSAIDs.

Celecoxib is indicated for familial adenomatous polyposis (FAP), which is not addressed in the current PA criteria for COX-2 inhibitors. Patients with FAP have obtained celecoxib from the NMOP through the PA appeal process. The committee agreed that the PA criteria should be revised to address FAP. The PEC will collaborate with DSCP and Merck-Medco to revise the PA criteria.

C. *Etanercept* – As a result of the "ERA" study, etanercept is now indicated for reducing signs and symptoms and delaying structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA). The PEC will collaborate with DSCP and Merck-Medco to revise the PA criteria for etanercept to properly address the expanded indication.

D. *Antifungals for onychomycosis (terbinafine, itraconazole)* – The PA for terbinafine and itraconazole for onychomycosis started 1 Jul 00 in the NMOP.

E. *Prior authorization portability process* – LTC Don De Groff reported that when the Prescription Data Transaction Service (PDTS) service is completely implemented, it will provide the capability to communicate prior authorization approvals across drug distribution channels (MTF pharmacies, NMOP, and retail pharmacies).

18. BENEFIT DETERMINATION FOR FERTILITY AGENTS – According to the Code of Federal Regulations and TRICARE policy, fertility drugs are not a covered benefit when used to assist in non-coital reproduction methods. The committee agreed with CDR Terry Egland's recommendation that prescriptions for the injectable gonadotropins (follitropin alfa, follitropin beta, urofollitropin, and menotropins) should be reviewed to determine benefit coverage.

19. PROTON PUMP INHIBITORS – Bill Hudson (Humana) initially proposed that a 90-day quantity limit be established for proton pump inhibitors (PPIs) to curb inappropriate long-term use. Committee members pointed out that extended use of PPIs does not necessarily indicate inappropriate care, so a 90-day quantity limit might impede access to appropriate care. The committee agreed with Mr. Hudson's suggestion to appoint a subcommittee to study this issue and offer recommendations at the next meeting. Subcommittee members are Bill Hudson, MAJ George Jones, LTC Judith O'Connor, MAJ Mickey Bellemin, and MAJ Ed Zastawny (PEC).

20. REPORT OF THE SUBCOMMITTEE ON QUANTITY LIMITS FOR TOPICALS – Bill Hudson reported frequency distributions of quantities dispensed per prescription for the topicals and a number of other high-volume drugs that are subject to quantity limits. Committee found that the current quantity limits appear to be appropriate.

21. CONTROLLED DISTRIBUTION OF ALENDRONATE (FOSAMAX) 40 MG (FOR PAGET'S DISEASE) – The committee was informed that Merck intends to implement a Paget's Disease Patient Support Program that includes enrollment of patients and exclusive distribution of alendronate (Fosamax) 40 mg through the specialty services pharmacy, CVS ProCare. Numerous issues regarding payment for prescriptions, patient enrollment, privacy concerns, etc., will have to be worked out in order for this program to be implemented for DoD patients.

22. CONTROLLED DISTRIBUTION OF DOFETILIDE (TIKOSYN) – Because of specialized educational requirements mandated by the FDA, this drug is only available for outpatient use through a single specialty pharmacy in the U.S. (Statlander's Pharmacy in Pittsburgh). LTC Bill Davies agreed to work with TMA contracting and policy officials and the MCSCs to address the issue of payment for dofetilide for patients in the retail network. Establishment of procedures for supplying and paying for dofetilide for MTF patients will likely require coordination between the pharmacy consultants/specialty leaders and resource management officials for each service. Dofetilide was excluded from the NMOP formulary at the last meeting.

23. CONSIDERATION OF COMBINATION DRUGS FOR THE NMOP – The committee agreed that newly marketed combination products should not be automatically added to the NMOP formulary, but should go through the normal evaluation process for addition to the formulary. If an acute need requires immediate attention, the issue should be referred to the co-chairs for an interim decision. COL Remund commented that the committee should evaluate the status of combination products with regard to the BCF at the next meeting.

24. ADJOURNMENT – The meeting adjourned at 1630 hours. The next meeting will be held 15 Nov 00 at a location to be determined. All agenda items should be submitted to the co-chairs no later than 15 Oct 00.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List Of Appendices

Appendix A: Formulary Changes

1. BCF Changes
   A. Additions to the BCF
      1) Ramipril (Altace; Monarch) (See Paragraph 7.)
   B. Changes and Clarifications to the BCF
      1) The BCF listing for "oxycodone 5 mg /acetaminophen 325 and 500 mg" was changed to "oxycodone/acetaminophen 5/325 mg ***and/or*** 5/500 mg." MTFs may decide to have one or both combinations on their formularies. (See Paragraph 9.)
      2) The BCF listing for fluoxetine was changed to specify that MTFs are not required to have the Sarafem brand of fluoxetine on their formularies. (See Paragraph 14C.)

2. NMOP Formulary Changes
   A. *Additions to the NMOP Formulary* (See Paragraph 14A.)
      1) Triamcinolone acetonide nasal spray (Tri-Nasal; Muro Pharma)
      2) Zonisamide capsules (Zonegran; Elan)
      3) Meloxicam tablets (Mobic; Boehringer-Ingelheim/Abbott).
      4) Pemirolast potassium ophthalmic solution (Alamast; Santen)
      5) Testosterone gel (Androgel; Unimed Pharma)
   B. *Exclusions from the NMOP Formulary* (See Paragraph 14B.)
      1) Linezolid injection, tablets, and oral suspension (Zyvox; Pharmacia & Upjohn),
   C. *Changes to the NMOP Preferred Drug Program*
      1) Deletion of non-preferred/preferred pair for cilostazol/pentoxifylline (See Paragraph 15.)
      2) Addition of meloxicam to NMOP Preferred Drug Program as a brand name NSAID (See Paragraph 14A3.)
      3) Discontinuation of the non-preferred/preferred drug pair for enalapril/lisinopril as soon as generic enalapril is available at a price that is competitive with other ACE inhibitors. (See Paragraph 15.)

3. Quantity Limit Changes (NMOP and retail network)
   A. Quantity limits for triamcinolone acetonide nasal spray (Tri-Nasal; Muro Pharma) were established: 6 bottles (45 gm) per 90 days in the NMOP and 2 bottles (15 gm) per 30 days in the retail network. (See Paragraph 14A1.)
   B. Quantity limits for ondansetron oral dissolving tablets (Zofran ODT) were clarified to be the same as quantity limits for ondansetron tablets (Zofran): 45 tablets per 90 days in the NMOP and 15 tablets per 30 days in the retail network for both the 4- and 8-mg tablets. (See Paragraph 4.)

Appendix A continued: Formulary Changes

4. Changes to the Prior Authorization Program (NMOP and retail network)
   A. Clarification of TRICARE policy caused discontinuation of the PA for COX-2 inhibitors in the retail pharmacy network. The COX-2 inhibitor PA will continue in the NMOP. (See Paragraphs 16 and 17B.)
   B. The COX-2 inhibitor PA in the NMOP will be revised to address the use of celecoxib for familial adenomatous polyposis. (See Paragraph 17B.)
   C. The etanercept PA in the NMOP and retail network will be revised to address the newly expanded indication of etanercept for reducing signs and symptoms and delaying structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA). (See Paragraph 17C.)

Appendix B: Items to Be Addressed at the Next Meeting

1. Report of the subcommittee to develop standard procedures for MTFs to request BCF changes and propose agenda items for the DoD P&T Committee. Subcommittee members include: MAJ George Jones (chair), MAJ Barbara Roach (PEC), MAJ Brett Kelly, CDR Matt Nutaitis, MAJ Mickey Bellemin, LTC Judith O'Connor.

2. Clinical review for $5HT_1$ receptor agonists for migraine ("triptans") – PEC

3. Price quotes for oral triptans obtained through a blanket purchase agreement request for quote – DSCP

4. Clinical review for thiazolidinediones ("glitazones") – PEC

5. Clinical review for oral inhaled corticosteroids – PEC

6. Clinical review for nasal inhaled corticosteroids – PEC

7. Clinical review for leutinizing hormone releasing hormones (LHRHs) - PEC

8. Report from the managed care support contractors regarding usage of linezolid in the retail network

9. Report of the subcommittee to study quantity limits for proton pump inhibitors. Subcommittee members include: Bill Hudson, MAJ George Jones, LTC Judith O'Connor, MAJ Mickey Bellemin, MAJ Ed Zastawny (PEC).

10. Controlled distribution of alendronate (Fosamax) 40 mg (for Paget's Disease)

11. Controlled distribution of dofetilide (Tikosyn)

12. Combination drugs on the BCF and NMOP Formulary

13. NMOP preferred drug program standing report – CDR Mark Brouker (PEC)

14. NMOP prior authorization program standing report – MAJ Mickey Bellemin, Shana Trice (PEC)

Appendix C: National Mail Order Pharmacy (NMOP) Preferred Drug Program Summary

Summary of Switch Rates and Estimated Cost Avoidance, Jun 99 – Jun 00*

Non-Preferred Drug	Preferred Drug	Switch Rate	Estimated Cost Avoidance	Total Number of Attempted Provider Contacts	Estimated Cost Avoidance per Attempted Provider Contact	Annualized Estimated Cost Avoidance
Cardizem CD Dilacor XR Diltia XT Diltiazem XR	**Tiazac**	68%	$466,128	4751	$98	$430,272
Procardia XL	**Adalat CC**	53%	$358,233	1963	$182	$330,722
Lodine XL Relafen Voltaren XR Daypro Naprelan	**Generic NSAIDs**	33%	$461,867	5502	$84	$426,338
H2 Blockers	**Generic ranitidine**	38%	$164,996**	1740	$95	$282,679
Enalapril	**Zestril**	45%	$92,854**	1704	$54	$222,850
Pletal	**Generic pentoxifylline**	11%	$1682	169	$10	$4036
Ditropan XL Detrol	**Generic oxybutynin**	29%	$112,269	3912	$30	$103,633
		Total	**$1,658,031**	**19741**	**$87**	**$1,800,530**

* The anti-herpes data are not presented because the new anti-herpes strategy of calling only on prescriptions for valacyclovir and famciclovir for chronic use (>30-day supply) was not implemented until 1 July 00.

** H2 blockers and enalapril→lisinopril implemented Dec 99 and Feb 00, respectively. Data and cost avoidance estimate in table is from date of implementation through Jun 00.

Appendix C continued: National Mail Order Pharmacy (NMOP) Preferred Drug Program Summary

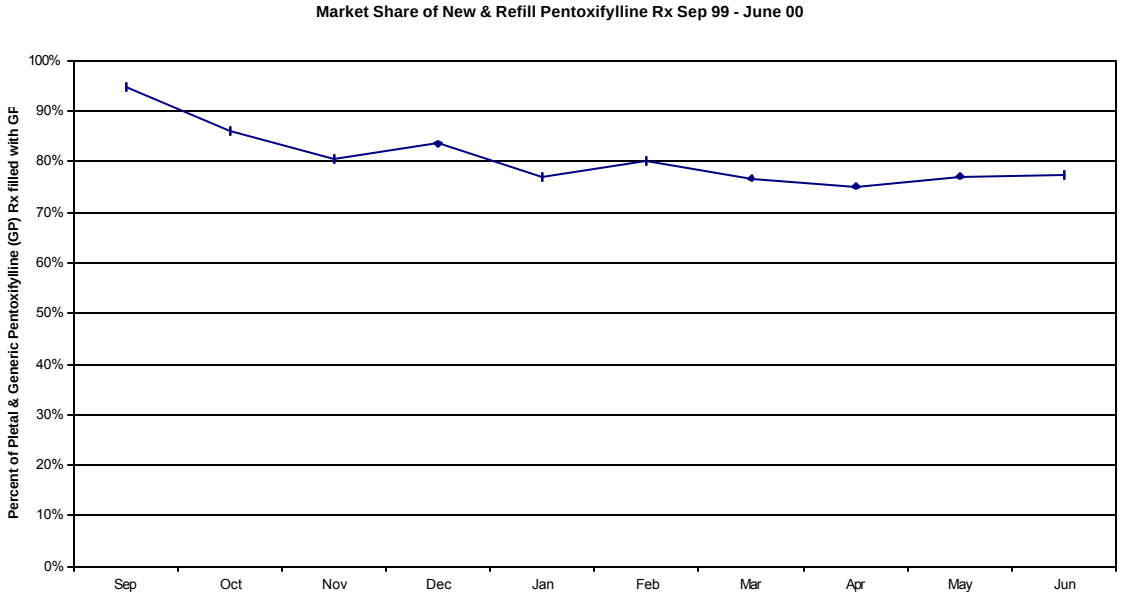
Summary of Switch Rates & Estimated Cost Avoidance for Pentoxifylline/Cilostazol, Feb 00 – Jun 00

Generic pentoxifylline was designated as a preferred drug in NMOP in August 99. Pletal (cilostazol) was designated as a non-preferred drug. Implementation began in February 2000.

Prescriptions for Non-Preferred Anti-Claudication Drugs in NMOP, Feb 00 – June 00[1]						
Month	**Feb 00**	**Mar 00**	**Apr 00**	**May 00**	**Jun 00**	**Feb 00- Jun 00**
New Rxs Received	23	33	32	41	40	169
Prescriber Contacts	21	28	26	37	38	150
Switches	5	0	3	4	6	18
Switch rate[2]	21%	0%	9%	10%	15%	11%

1 From Merck-Medco reports "NMOP Switch Report," "DoD Target Drug Report," and "DoD Prescription Volume Report" covering February through 30 June 00.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic pentoxifylline.

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Feb 00	Mar 00	Apr 00	May 00	Jun 00	**Feb 00 – Jun 00**
Monthly Cost avoidance	$466	$0	$280	$457	$679	$1682

***** Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the stated prescriptions had not been switched. Derived by multiplying the number of reported prescriptions switched for each target drug times the difference in average cost per prescription (target drug – pentoxifylline). [Note: this is a different methodology than used for other drugs and is due to difficulties in establishing a baseline percentage of market share for each of these drugs and uncertainty as to the validity of carrying percentages through to subsequent months.]

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MCCS-GPE 11 May 2000

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 11 May 2000, at Fort Sam Houston, TX.

2. MEMBERS PRESENT:

CDR Terrance Egland, MC	Co-chair
COL Daniel D. Remund, MS	Co-chair
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Daniele Doyle, DAC	Army
CDR Matt Nutaitis, MC	Navy
LCDR Kevin Cook, MSC	Navy
COL (select) Bill Sykora, MC	Air Force
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs (alternate)
LTC Greg Russie, BSC	Joint Readiness Clinical Advisory Board (alternate)
LTC Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest

OTHERS PRESENT:

CAPT Charlie Hostettler, MSC	DoD Pharmacy Program Director, TMA
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
LTC Gary Blamire, BSC	TRICARE Lead Agent Office (Region 6)
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center (PEC)
MAJ Barbara Roach, MS	DoD Pharmacoeconomic Center (PEC)
MAJ Jennifer Styles, MS	Pharmacy Practice Resident, BAMC
MAJ Brett Kelly, MS	TRICARE Lead Agent Office (Region 1)
LCDR Mark Richerson, MSC	DoD Pharmacoeconomic Center (PEC)
SFC Tom Bolinger	DoD Pharmacoeconomic Center (PEC)
Paul Vasquez	Defense Supply Center Philadelphia (DSCP)
Vinny Valinotti	Defense Supply Center Philadelphia (DSCP)
Shana Trice, DAC	DoD Pharmacoeconomic Center (PEC)
Eugene Moore, DAC	DoD Pharmacoeconomic Center (PEC)
Mark Petruzzi	Merck-Medco
Liz Scaturro	Merck-Medco

3. ADMINISTRATIVE ISSUES:

The minutes from the last meeting were accepted as written.

4. OLD BUSINESS

A. Review of Interim Decisions

1) The committee co-chairs revised the National Mail Order Pharmacy (NMOP) and retail pharmacy network quantity limits on an interim basis to meet timelines for the alpha test of the Pharmacy Data Transaction Service (PDTS). The committee agreed with the revised quantity limits. The revised quantity limits will be posted on the PEC website. Although the quantity limits do not currently apply to military treatment facility (MTF) pharmacies, it is likely that the NMOP quantity limits will apply to MTF pharmacies sometime in the future.

2) The committee co-chairs made an interim decision to suspend the designation of Nitro-Dur as the preferred brand of nitroglycerin patch in the NMOP when it was discovered that the Nitro-Dur patches do not cost less than other brands of nitroglycerin patches. Nitro-Dur packages designated for institutional use have low DAPA prices, but Merck-Medco cannot legally dispense these patches through the NMOP. The committee agreed with the co-chairs' interim decision. A preferred brand of nitroglycerin patch is no longer designated in the NMOP.

B. *Update on the Pharmacy Data Transaction Service (PDTS)*—COL Remund updated the committee on deployment and progress of the PDTS project. The alpha deployment at Wright-Patterson AFB successfully tested the PDTS process. Enhancements are required to the CHCS software prior to additional deployments of PDTS within the direct care system.

CAPT Hostettler commented that PDTS represents a major DoD initiative for medication error prevention and patient safety.

C. National Mail Order Pharmacy (NMOP) Preferred Drug Program

1) CDR Brouker reported the switch rates and estimated cost avoidance for the preferred drug program in the NMOP (see Appendix A). The NMOP Preferred Drug Program is estimated to result in $1.56 million in annual cost avoidance for DoD.

2) *Antiviral Drugs for Herpes (acyclovir, valacyclovir, famciclovir)*—The preferred drug program for this class currently has an estimated cost avoidance per attempted provider contact of only $8, compared to an average of $76 for the entire NMOP preferred drug program. However, if the switch program for this drug class were to be targeted to chronic suppression of herpes, the estimated cost avoidance per attempted provider contact would increase to approximately $86. The cost to DoD for a 90-day regimen of acyclovir is approximately $7, compared to $403 for famciclovir and $183 for valacyclovir. Acyclovir is given twice daily for chronic suppression, compared to once daily for valacyclovir and twice daily for famciclovir. The committee approved the proposal to request switches to acyclovir only on famciclovir and valacyclovir prescriptions that are written for more than a 30-day supply (chronic therapy).

The committee discussed the following additional proposal: *When prescriptions for chronic therapy with famciclovir or valacyclovir are received by the NMOP, Merck-Medco would call the prescriber to offer a switch to acyclovir. If the prescriber declined to switch from famciclovir to acyclovir, Merck-Medco would then suggest the famciclovir be switched to valacyclovir.* Mark Petruzzi (Merck-Medco) will report to the co-chairs by July 17th regarding the feasibility of the additional proposal. In the interim, Merck-Medco will ask prescribers to switch prescriptions for chronic therapy with famciclovir or valacyclovir to acyclovir.

D. *Report of the Subcommittee on Quantity Limits for Topicals*—The committee approved the quantity limits presented by the subcommittee for the five high-cost topicals identified at the last meeting: imiquimod (Aldara); calcipotriene (Dovonex); altitretinoin (Panretin); becaplermin (Regranex); and tazarotene (Tazorac) (See Appendix B). The subcommittee will report on the frequency distribution of quantities dispensed per prescription for these drugs at the next meeting. An interim report is due to the co-chairs by 17 Jul 00.

E. *Report of the Growth Hormone Subcommittee*—The committee reviewed the data presented by Bill Hudson (Humana) to justify a prior authorization program for growth hormone in the NMOP and the retail network. Mr. Hudson estimated a 1% denial rate for growth hormone prescriptions. The committee decided not to institute a prior authorization program because the inconvenience to prescribers and patients outweighs the relatively small potential for cost avoidance.

F. *Update on the Advances in Medical Practice (AMP) Program*—COL Remund reported that AMP funds have been distributed to the service level. The pharmacy consultants/specialty

leaders are working with the service resource management officers to devise procedures for reimbursing MTFs for expenditures on drugs covered by the AMP program.

G. *Update on Program Budget Decision 041*—The DOD P&T Committee added several drugs to the BCF at the Jan 00 interim meeting. Per DoD Health Affairs Policy 98-034 (Policy for Basic Core Formulary and Committed Use Requirements Contracts), all BCF drugs must be included on all MTF formularies.

H. *Cost-efficiency of prior authorizations in the NMOP*—MAJ Bellemin provided a verbal report to the committee. The committee directed the co-chairs to appoint a subcommittee to 1) develop a standard written report for prior authorization data, and 2) explore methods to quantify the clinical, economic, and humanistic outcomes associated with the prior authorization program. The subcommittee will include members from DSCP, PEC, Merck-Medco, and the Managed Care Support Contractors. A report is due to the co-chairs by 17 Jul 00.

I. *Prior authorization for oral antifungals for onychomycosis*—The co-chairs presented prior authorization criteria for terbinafine for the treatment of onychomycosis. The criteria require the confirmation of an active fungal infection to ensure the clinical appropriateness of therapy for onychomycosis.

Bill Hudson reported that the vast majority of use of itraconazole in Region 3 and 5 is for onychomycosis and proposed that the prior authorization also apply to itraconazole for the treatment of onychomycosis. The committee agreed that the prior authorization program should apply to itraconazole as well as terbinafine in the treatment of onychomycosis.

J. *Determining benefit coverage of fertility agents*—According to the Code of Federal Regulations and TRICARE policy, fertility drugs are not a covered benefit when used to assist in non-coital reproduction methods. Paul Vasquez (DSCP) reported that a recent contract modification to the NMOP Statement of Work (SOW) reiterated the original SOW requirement for the contractor to fill prescriptions in accordance with TRICARE policy. Merck-Medco will develop a process to ensure that prescriptions for fertility agents are dispensed to DoD beneficiaries in accordance with TRICARE policy. Since this was an original requirement of the contract, there will be no additional payment by DoD for this process.

K. *Revising prior authorization forms to include education for providers*—The committee endorsed the recommendation by LTC Judith O'Connor that the prior authorization program should include an educational component. The committee decided that the prior authorization request forms should briefly explain why the drug requires prior authorization. The PEC will revise the prior authorization request forms accordingly.

L. *Portability of Prior Authorizations*—MAJ Mickey Bellemin reported that portability of prior authorization approvals across the retail network and NMOP will eventually be accomplished through PDTS. CAPT Hostettler commented that the managed care support contractors are still exploring other options to achieve portability of prior authorization approvals.

5. NEW BUSINESS

A. National Pharmaceutical Contracts

1) *Contracts awarded since last meeting*:

a. The VA National Acquisition Center (NAC) awarded DoD/VA joint contracts to Able Laboratories for salsalate 500 and 750 mg tablets (effective date 15 Mar 00) and to Becton Dickinson for insulin syringes with needles (effective date 1 May 00). All DoD MTFs and all VA facilities that use these products are required to purchase the contract brands. The contract for insulin syringes with needles also applies to the NMOP.

b. Defense Supply Center Philadelphia (DSCP) awarded a DoD/VA contract to Novartis Consumer Health for nicotine patches (effective date 1 Jun 00). All DoD MTFs and VA facilities that use a 3-step nicotine patch are required to purchase the contract brand of this product. **Please note:** The contract does not mandate inclusion of nicotine patches on the BCF. MTFs are not required to add nicotine patches to their formularies.

2) *Financial Impact of National Pharmaceutical Contracts*— The PEC uses prime vendor purchase data to quantify the financial impact of national pharmaceutical contracts. COL Remund presented slides showing the cost avoidance associated with major DoD and DoD/VA contracts for FY99 and the first 5 months of FY00. These slides will be published on the PEC website at **www.pec.osd.ha.mil**.

COL Remund also reported on recent voluntary price reductions by Merck for simvastatin (decrease from $0.66 to 0.62 for the 10 mg tablet, $1.07 to $0.75 for the 20 mg tablet, and from $1.07 to $1.00 for the 40 mg tablet). The price reduction will yield approximately $10 million annually in additional cost avoidance for MTFs.

3) *Returned Goods Contract* – DSCP has the lead on developing the solicitation for a joint DoD/VA contract for processing returned goods.

4) *Second Generation Antihistamines*—The committee (on a vote of ten in favor with two abstentions) decided that DoD should not seek a joint DoD/VA closed class contract for a single once-daily, non-sedating antihistamine because:

a. The provisions of a closed class contract are not compatible with clinical practice regarding this drug class. A relatively large percentage of patients will not respond adequately to a given antihistamine. If a patient does not respond adequately to an antihistamine, it is common clinical practice to try a different antihistamine. Under a closed class contract, non-contracted drugs can be used only after a prior authorization or non-formulary request process is completed. Implementation of a

closed class contract for a single agent in this class would place an unacceptably large administrative burden on DoD beneficiaries, prescribers, and pharmacies.

b. A closed class contract requires patients to be switched from non-contracted drugs to the contracted drug. Converting patients from non-contracted drugs to contracted drugs is much more difficult to accomplish in the Military Health Care System than in the VA because of major differences in pharmacy benefit designs and drug distribution systems.

B. *FY00 National Defense Authorization Act*—CAPT Hostettler briefed the committee on the ongoing efforts to implement the provisions pertaining to the Uniform Formulary and the DoD P&T Committee.

C. *BCF and NMOP formulary issues:*

1) *Added to the NMOP Formulary*—The following drugs were added to the NMOP Formulary. None of these drugs were added to the BCF.

a. Levetiracetam tablets (Keppra; UCB Pharma) approved 30 Nov 99 as adjunctive therapy for partial onset seizures in adults

b. Ciclopirox topical solution (Penlac Nail Lacquer; Dermik/Aventis) approved 17 Dec 99 for mild to moderate onychomycosis

c. Nedocromil sodium ophthalmic solution, 2% (Alocril; Allergan) approved 8 Dec 99 for itch associated with allergic conjunctivitis

d. Cevimeline HCl capsules (Evoxac; Snowbrand Pharma) approved 11 Jan 00 for dry mouth in Sjögrens Syndrome

e. Alosetron tablets (Lotronex; Glaxo) approved 9 Feb 00 for women with diarrhea-predominant irritable bowel syndrome (IBS). Alosetron has been tested largely in women, who make up the majority of patients complaining of IBS in the U.S. In addition, plasma concentrations of alosetron appear to be influenced by gender (27% lower in men). Because there is currently no evidence of efficacy in male patients, coverage of this drug in the NMOP will be limited to female patients. Alosetron will be excluded from the NMOP formulary when prescribed for male patients.

f. Rivastigmine capsules (Exelon; Novartis) approved 24 Apr 00 for mild to moderate Alzheimers disease

g. Sotalol (BetapaceAF; Berlex) approved 22 Feb 00 for maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Sotalol was previously marketed (as Betapace) for ventricular arrhythmias only. Betapace AF is chemically identical to Betapace but is supplied in unit-of-use packages containing specialized labeling for patients with atrial fibrillation (analogous to dual packaging of bupropion as Zyban and Wellbutrin). The FDA recommends that patients

currently receiving Betapace for atrial arrhythmias be converted to BetapaceAF in order to receive appropriate patient information. The NMOP will fill prescriptions for these products as written, e.g., BetapaceAF for "BetapaceAF" and Betapace (or the soon-to-be-available AB-rated generic) for "Betapace."

2) *Excluded from the NMOP Formulary*—Dofetilide (Tikosyn; Pfizer), approved 1 Oct 99 for maintenance of normal sinus rhythm in atrial fibrillation/flutter, was excluded from the NMOP formulary and will not be available through the NMOP. Dofetilide was NOT added to the BCF. Because of the potential for dofetilide to cause torsade de pointes, a serious and potentially lethal ventricular arrhythmia, the drug is subject to a restricted distribution process. The FDA requires documentation that prescribers and inpatient pharmacies have received education concerning the algorithm for initiating the drug, which must be started in a monitored inpatient setting. Maintenance supplies for outpatient use are currently dispensed only through Statlander's Pharmacy in Pittsburgh. The NMOP has no mechanism to refer prescriptions to Statlander's and turnaround time is a major concern. Mark Petruzzi (Merck-Medco) stated that a joint venture might occur between Merck-Medco and a specialty pharmacy company, which may be able to provide this type of medication in the future. Merck-Medco will report back to the committee if it becomes possible to provide dofetilide through the NMOP.

3) *Clarification of Antihemophilic Factors on the NMOP Formulary Covered Injectables List*—The committee intends that all antihemophilic factors be available through the NMOP. The committee clarified the current listing on the NMOP Covered Injectables List to read " *Antihemophilic Factors (including Factor VII, Factor VIII, Factor IX, Factor IX Complex, and Anti-Inhibitor Factor Complex).*"

4) *Catastrophic Drug Accounts*—The preceding discussion of antihemophilic factors led to a discussion of catastrophic drug accounts for MTFs. Extremely high cost specialty medications, such as the antihemophilic factors, cause extreme strain on the budgets of smaller MTFs. The issue of catastrophic drug accounts is beyond the purview of the committee, so it was referred to COL Mike Heath as chairman of the Pharmacy Board of Directors.

5) *Nasal Corticosteroids (BCF)*—LCDR Mark Richerson (PEC) presented an analysis of MTF prescription data that showed weighted averages of 3.57 sprays per day for fluticasone nasal spray and 3.95 sprays per day for mometasone nasal spray. Based on DAPA prices of $11.12 per fluticasone inhaler and $10.49 per mometasone inhaler, fluticasone is slightly more cost-effective than mometasone. Since mometasone does not offer any advantage in cost-effectiveness, the committee decided that fluticasone should remain as the only nasal corticosteroid inhaler on the BCF.

6) *Consideration of Niaspan (niacin extended release; Kos Pharma) for the BCF*—The committee decided not to add Niaspan to the BCF because it does not offer sufficient clinical advantage over immediate release niacin to justify the large increase in cost.

The committee made its decision based on the following comparison of Niaspan and immediate release niacin.

a. Niaspan and immediate release niacin have similar safety profiles. During clinical trials, increases in liver enzymes with Niaspan were comparable to those occurring with immediate release niacin. Required monitoring of liver function tests is the same for Niaspan and immediate release niacin.

b. It is unclear whether Niaspan offers a clinically meaningful advantage in patient tolerability over immediate release niacin. In a comparative study, 42% of patients on Niaspan and 39% of patients on immediate release niacin experienced flushing. However, the Niaspan group averaged only 1.9 episodes per month compared to 8.6 episodes per month for the immediate release niacin group. In a study comparing Niaspan to placebo, 88% of patients taking Niaspan 1000 mg per day and 83% of patients taking Niaspan 2000 mg per day experienced flushing, compared to 20% of placebo patients. In a 96-week open label study, 75% of Niaspan patients experienced flushing and 47% of Niaspan patients dropped out of the study for reasons related to the drug (although the specific reasons were not identified in the study).

c. At equivalent doses, Niaspan and immediate release niacin have a similar effect on lipid levels.

d. Depending on dosage, Niaspan costs about 20 to 30 times more than immediate release niacin.

7) Review of ophthalmic glaucoma agents for the BCF—CDR Matt Nutaitis, an ophthalmologist and glaucoma specialist, presented recommendations based on his own experience; input from glaucoma specialists from all three services; current usage in DoD; and the relative safety, tolerability, efficacy, and cost of available ophthalmic agents for the treatment of glaucoma. (See Appendix C.) The committee adopted the following recommendations:

Remove the following agents from the BCF:

- Betaxolol Ophthalmic Suspension
- Dorzolamide Ophthalmic Solution
- Pilocarpine Ophthalmic Gel

Add the following agent to the BCF:

- Brimonidine Ophthalmic Solution (Alphagan; Allergan)

8) *Consideration of metronidazole vaginal gel for the BCF*—The committee added metronidazole vaginal gel to the BCF to provide an alternative to clindamycin vaginal cream in pregnant women with symptomatic bacterial vaginosis who are at low risk for premature birth. The Centers for Disease Control and Prevention (CDC) 1998

Guidelines for Treatment of Sexually Transmitted Diseases state that for treatment of pregnant women, "the use of clindamycin vaginal cream during pregnancy is not recommended, because two randomized trials indicated an increase in the number of preterm deliveries among pregnant women who were treated with this medication." Clindamycin vaginal cream and metronidazole vaginal gel are similar in cost. Clindamycin vaginal cream remains on the BCF.

9) *Clarification of oxycodone/acetaminophen listing on BCF*— The approval in mid-99 of three new strengths for oxycodone/acetaminophen (Percocet 2.5/325, 7.5/500, 10/650; Endo) has led to questions by MTFs about which strengths of Percocet they are required to carry. The committee decided that the incremental clinical value of the new strengths was likely to be minimal. Because including the new strengths on the BCF would increase accounting and storage requirements for these controlled drugs, the committee did not opt to add them to the BCF. The committee decided that the BCF should specify that MTFs must have oxycodone/acetaminophen in the 5/325 and 5/500 mg strengths on their formularies but are not required to have the 2.5/325, 7.5/500, and 10/650 mg strengths on their formularies.

10) *Status of angiotensin-converting enzyme inhibitors (ACEIs) on the BCF*—The committee discussed at length a proposal to add ramipril (Altace; Monarch) to the BCF as a second long-acting ACEI. ACEIs already on the BCF are the short-acting agent captopril and the long-acting agent lisinopril.

Arguments in favor of the proposal to add ramipril to the BCF included:

- ACEIs tend to be underutilized. Addition of another ACEI to the BCF would ensure uniform availability of another agent within a class of drugs that is known to provide significant clinical benefits at a reasonable cost.
- Significant clinical benefits were demonstrated in a recent study where patients at high risk of cardiovascular events but without existing heart failure were treated with ramipril. The Heart Outcomes Prevention Evaluation (HOPE) study (*NEJM* 342(3):145-53; 20 Jan 00) and the MICRO-HOPE diabetic substudy (*Lancet* 355(9200):253-9; 22 Jan 00)] demonstrated significant decreases in the rate of death, myocardial infarction, and stroke in patients receiving ramipril; as well as significant decreases in the risk of overt nephropathy in diabetic patients.
- The addition of ramipril might encourage price competition within the ACEI drug class because the DAPA price of $.12 per tablet for all strengths of ramipril is $.02 less than the $.14 price per tablet for all strengths of lisinopril.

Arguments against the proposal to add ramipril to the BCF included:

- Many MTFs already have more than one long-acting ACEI on their formularies, so the addition of ramipril to the BCF might not have any effect on the overall utilization of ACEIs. Ramipril currently has very little market share in DoD MTFs.
- It is not known if other ACEIs would achieve the same clinical benefits as ramipril achieved in the HOPE study. These results could possibly represent a class effect of ACEIs.

- Greater price competition could probably be achieved by selecting a second long-acting ACEI through a contracting initiative or incentive price agreement.

COL Remund informed the committee that contracting officials have not yet delineated a method for contracting for a BCF selection among different chemical entities in an open drug class. All the open class contracts established to date have involved the selection of a specific brand of a single chemical entity that is marketed by more than one company. The selection of a second long-acting ACEI for the BCF would involve competition between different chemical entities. The committee does not want to close the ACEI drug class on the BCF, so a closed class contract is not a suitable method for selecting a second long-acting ACEI.

A motion to table the proposal to add ramipril to the BCF was defeated by a vote of 5 in favor, 6 against, and one abstention. The committee subsequently approved the addition of ramipril to the BCF by a vote of 7 in favor and 5 against.

Following the meeting and prior to the preparation of the meeting minutes, committee members contacted the co-chairs to express their concerns about the committee's decision to add ramipril to the BCF:

- A committee member pointed out that the $.02 per tablet price advantage for ramipril over lisinopril might be at least partially negated if twice a day dosing is more common for ramipril than for lisinopril. A subsequent analysis of the frequency distributions of dosages observed by a large national PBM revealed that twice a day dosing is more common for ramipril than for lisinopril. Based on the dosage distribution, the DAPA price for ramipril, and the contract price for lisinopril; the average weighted daily costs differ by only $.009 ($0.147 for ramipril and $0.156 for lisinopril).
- A committee member expressed concern that the committee did not consider the possibility that the incidence of cough as an adverse effect may be higher for ramipril than for other ACEIs. The table of adverse effects for ACEIs in *Facts and Comparisons* shows a higher incidence of cough for ramipril than for all but one other ACEI. However, the data are pooled from separate studies and are not necessarily comparable.

In light of these concerns, the P&T Committee members approved a motion to rescind the addition of ramipril to the BCF by a vote of 9 in favor and 0 against (three committee members were on leave or temporary duty and could not be contacted).

11) *Status of oral contraceptive products (OCPs) on the BCF* (see Appendix D for a list of OCPs)—(Note: costs quoted in the following discussion are based on DAPA prices as of May 00; prices are for the 28-day packs if both 21- and 28-day packs are available)

a. Monophasic OCPs with 20 mcg ethinyl estradiol (EE): There is no BCF agent in this category. The committee made no selection or recommendation in this category.

b. *Monophasic OCPs with 30 mcg EE:* EE 30 mcg/0.3 mg norgestrel (e.g., Lo/Ovral, Low-Orgestrel) remains on the BCF. The current cost per cycle for both Lo/Ovral and Low-Ogestrel is $8.00. The committee added EE 30 mcg/1.5 mg norethindrone (Loestrin FE 1.5/30) to the BCF as an alternative that offers a significant economic advantage. The current cost per cycle for Loestrin FE 1.5/30 is $2.00.

c. *Monophasic OCPs with 35 mcg EE:* The 35 mcg EE/1 mg norethindrone combination (e.g., Necon, Norinyl, Ortho-Novum) remains on the BCF. Any brand containing this combination of ingredients may be used by MTFs to fulfill the BCF requirement. The committee recommended selection of a specific brand of 35 mcg EE/1 mg norethindrone for the BCF as a potential item for a contract or incentive price agreement.

The committee added EE 35 mcg/1 mg ethynodiol diacetate (e.g., Demulen, Zovia) to the BCF. Any brand containing this combination of ingredients may be used by MTFs to fulfill the BCF requirement. This agent was added because military providers said that the combination was clinically useful for patients with acne, and because it is less expensive than other oral contraceptives touted for use in patients with acne. The committee recommended selection of a specific brand of EE 35 mcg/1 mg ethynodiol diacetate for the BCF as a potential item for a contract or incentive price agreement.

d. *Biphasic OCPs*–There is no BCF agent in this category. There is very little use of biphasic products in DoD. The committee made no selection or recommendation in this category.

e. *Triphasic OCPs*—EE 30/40/30mcg/levonorgestrel 0.05/0.075/0.125 mcg remains on the BCF. Any brand containing this combination of ingredients may be used by MTFs to fulfill the BCF requirement (e.g., Tri-levlen, Triphasil, Trivora). The committee recommended selection of a specific brand of EE 30/40/30mcg / levonorgestrel 0.05/0.075/0.125 mcg for the BCF as a potential item for a contract or incentive price agreement.

The committee initially decided to remove EE 35 mcg/norethindrone 0.5/0.75/1 mg (Ortho-Novum 7/7/7) from the BCF based on a comparison of the DAPA price for Ortho-Novum 7/7/7 to the DAPA prices of other triphasic OCPs. Subsequent to the meeting, additional information concerning the availability and pricing of Ortho-Novum 7/7/7 through the DSCP Centrally Managed Inventory Program (Depot) was brought to the attention of the co-chairs. The co-chairs made an interim decision to leave Ortho-Novum 7/7/7 on the BCF. The BCF status of Ortho-Novum 7/7/7 will be reconsidered when more definitive information is available concerning the pricing, usage volume, and prospective status of Ortho-Novum 7/7/7 as a depot stock item.

f. *Progestin-only OCPs ("mini-pills"):* The committee added 0.35 mg norethindrone (e.g., Micronor, Nor-Q.D) to the BCF to meet the needs of women who require a

progestin-only product. There were previously no progestin-only products on the BCF. The committee recommended selection of a specific brand of 0.35 mg norethindrone for the BCF as a potential item for a contract or incentive price agreement.

g. *Other OCPs:* Due to their infrequent use, OCPs with 50 mcg EE or mestranol as the estrogen component were not considered.

The committee requested that the PEC amend BCF listings on the PEC website to make it clear that the BCF does not currently specify any drug by trade name in this class. For example, the listing for 35 mcg EE/1 mg norethindrone means that any product containing this combination of ingredients is acceptable. The committee agreed that 28-day packages of oral contraceptives are preferable to 21-day packages because patients are more likely to remember to take the tablets on a daily basis.

12) *Status of narcotic pain medications on the BCF*—The committee was asked by an MTF to consider the addition of a long-acting oral narcotic analgesic to the BCF. The committee added extended release morphine tablets (MS Contin or its AB-rated generic equivalent) in the following strengths: 15-, 30-, and 60-mg. MS Contin is also currently available in 100- and 200-mg tablets, which are not included in the BCF listing. MTFs may add the 100- and 200-mg strengths to their local formularies if they so desire. The BCF listing does not include Oramorph SR, Kadian, or any other extended release morphine product other than MS Contin or AB-rated generic equivalents.

13) *Withdrawal of troglitazone and cisapride:* The committee discussed the withdrawal of troglitazone (Rezulin) and cisapride (Propulsid) from the market. Troglitazone is no longer available. Cisapride will continue to be available only through an investigational drug/limited access program once the manufacturer discontinues marketing (Jul 00) and existing stocks are exhausted. MTFs should be in the process of switching patients to alternative medications and identifying patients whose need for treatment with cisapride justifies pursuing approval through the limited access program.

7. ADJOURNMENT: The meeting adjourned at 1530 hours. The next meeting will be held on Thursday, 17 Aug 00 at a site to be determined. All agenda items should be submitted to the co-chairs no later than 17 Jul 00.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List Of Appendices

APPENDIX A: NMOP Preferred Drug Program Report

May 00 NMOP Preferred Drug Program Report

1. Extended Release Diltiazem

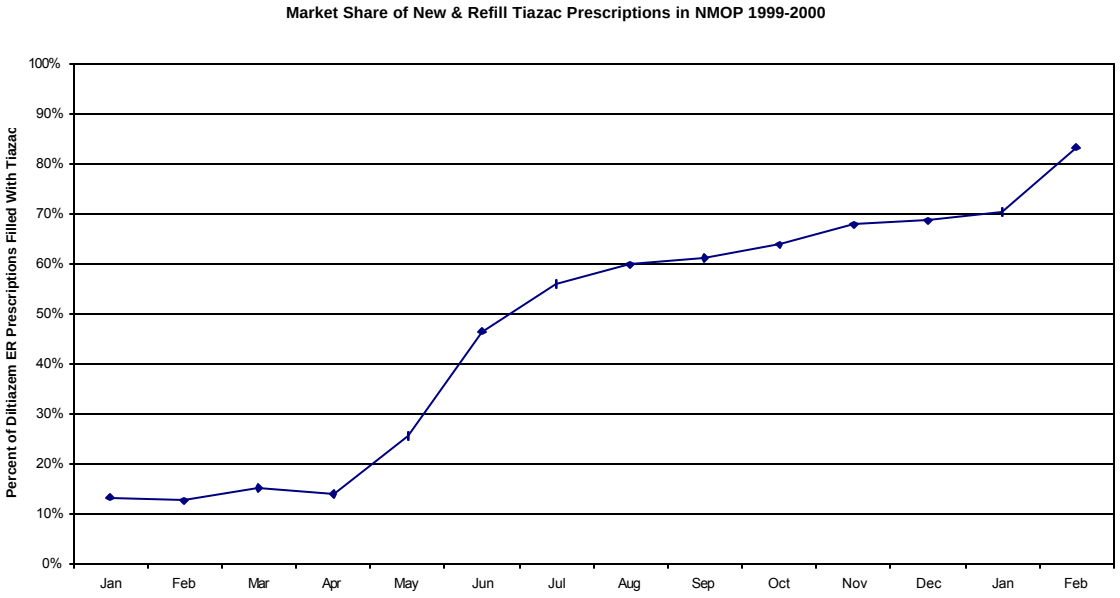
Tiazac was designated as the preferred diltiazem ER product in NMOP in May 99. Non-preferred diltiazems include Cardizem CD, Diltia XT, Dilacor XR, and generic diltiazem ER.

Table 1: Prescriptions for Non-Preferred Diltiazem ER products in NMOP, Jun 99 – Feb 00[1]

Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	**Jun 99-Feb 00**
New Rxs Received	720	661	573	395	328	291	346	155	178	**3647**
Prescriber Contacts	653	616	540	352	301	263	311	134	156	**3326**
Switches	514	495	434	255	215	189	217	97	116	**2532**
Switch rate[2]	71%	75%	76%	65%	66%	65%	63%	63%	65%	**69%**

1 From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 29 May 1999 through 29 February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to Tiazac

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Jun 99	Jul 99	Aug 99	Sep 99	Oct 99	Nov 99	Dec 99	Jan 00	Feb 00	**Jun 99-Feb 00**
Monthly Cost avoidance	$21,796	$27,287	$31,098	$29,017	$28,112	$34,592	$30,123	$33,877	$37,697	**$273,599**

*Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the prescriptions had not been switched. The figure for "would-have-been" expenditures is derived by multiplying the mean percentage of market share (by prescription; both new and refill) during Jan-Apr 99 for each drug by the total number of new and refill prescriptions in each month for all non-preferred and preferred drugs, and then multiplying this figure by the average cost per prescription for each drug, and summing for all non-preferred and preferred drugs.

2. Extended Release Nifedipine

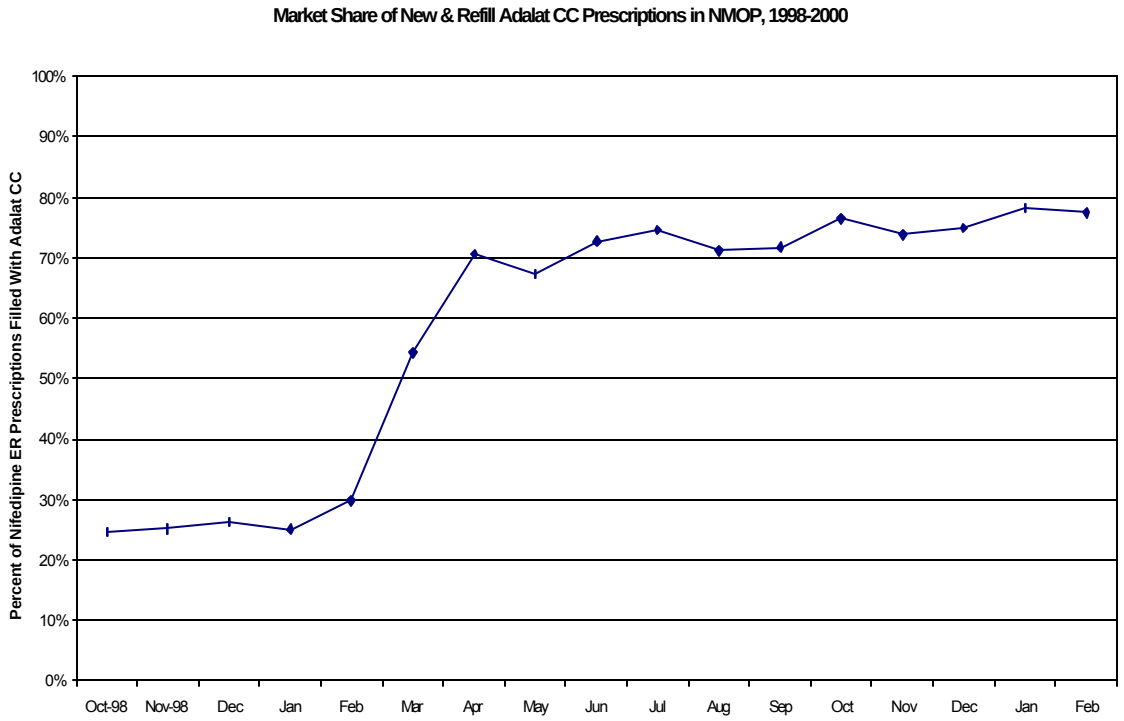
In Nov 98 the DOD P & T Committee selected Adalat CC as the preferred nifedipine ER product. Procardia XL is non-preferred.

Table 2: Prescriptions for Non-Preferred Nifedipine ER in NMOP, Jun 99 – Feb 2000[1]

Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Jun 99 – Feb 00
New Rxs Received	379	142	125	139	124	127	153	111	115	**1415**
Prescriber Contacts	345	132	102	120	114	101	129	99	105	**1247**
Switches	254	91	66	63	61	58	90	62	53	**798**
Switch rate[2]	67%	64%	53%	45%	49%	46%	59%	56%	46%	**56%**

1. From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 29 May 1999 through 29 February.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to Adalat CC.

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Jun 99	Jul 99	Aug 99	Sep 99	Oct 99	Nov 99	Dec 99	Jan 00	Feb 00	Jun 99 – Feb 00
Cost Avoidance	$27,494	$26,624	$24,962	$24,510	$27,938	$26,122	$24,173	$32,785	$27,030	**$241,638**

*Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the prescriptions had not been switched. The figure for "would-have-been" expenditures is derived by multiplying the mean percentage of market share (by prescription; both new and refill) during Oct – Nov 98 for each drug by the total number of new and refill prescriptions in each month for all non-preferred and preferred drugs, and then multiplying this figure by the average cost per prescription for each drug, and summing for all non-preferred and preferred drugs.

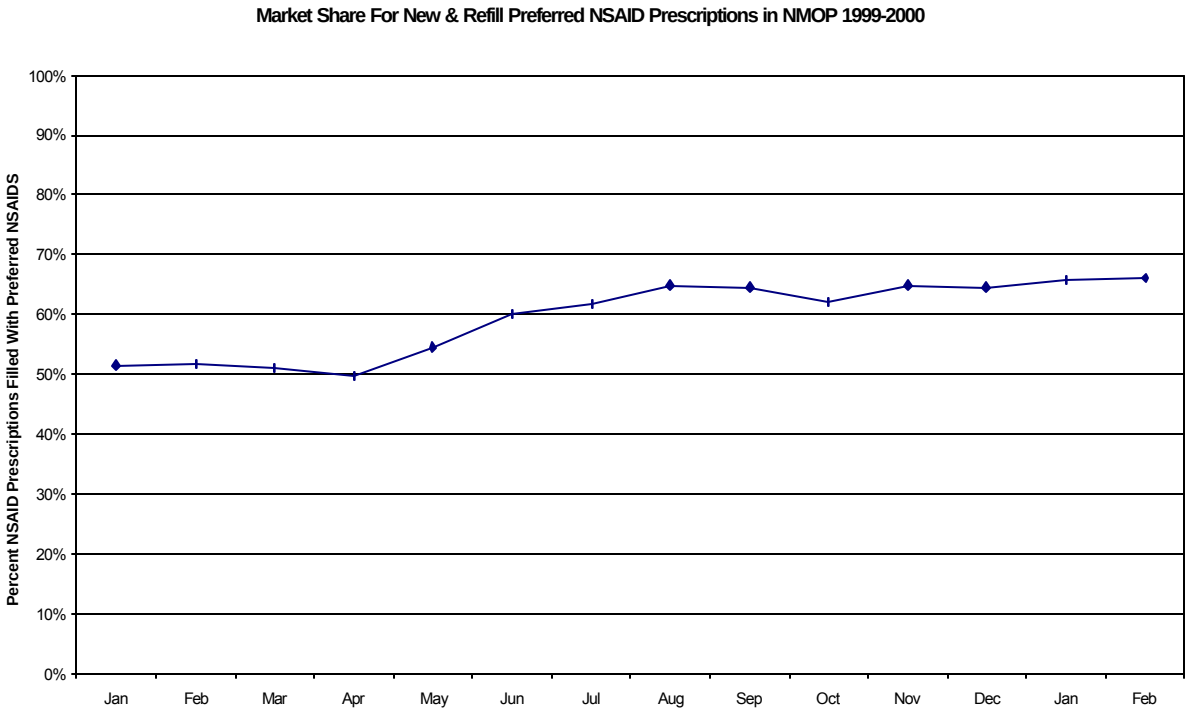
3. NSAIDS

Generic NSAIDs are preferred. Daypro, Relafen, Voltaren XR, Lodine XL, and Naprelan are non-preferred. Program started mid-May, 99

Table 3: Prescriptions For Non-Preferred NSAIDs in NMOP, Jun 99 – Feb 00[1]										
Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	**Jun 99 – Feb 00**
New Rxs Received	617	596	549	456	432	361	434	336	347	**4128**
Prescriber Contacts	525	504	492	385	367	304	384	309	314	**3574**
Switches	244	220	248	153	150	140	136	114	115	**1420**
Switch rate[2]	40%	37%	45%	34%	35%	39%	31%	34%	33%	**34%**

1 From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 29 May 1999 through 29 February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic NSAIDs.

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Jun 99	Jul 99	Aug 99	Sep 99	Oct 99	Nov 99	Dec 99	Jan 00	Feb 00	**Jun 99 – Feb 00**
Cost Avoidance	$21,771	$19,929	$27,670	$29,294	$25,052	$36,465	$29,364	$41,151	$35,260	**$342,206**

*Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the prescriptions had not been switched. The figure for "would-have-been" expenditures is derived by multiplying the mean percentage of market share (by prescription; both new and refill) during Jan – Apr 99 for each drug by the total number of new and refill prescriptions in each month for all non-preferred and preferred drugs, and then multiplying this figure by the average cost per prescription for each drug, and summing for all non-preferred and preferred drugs.

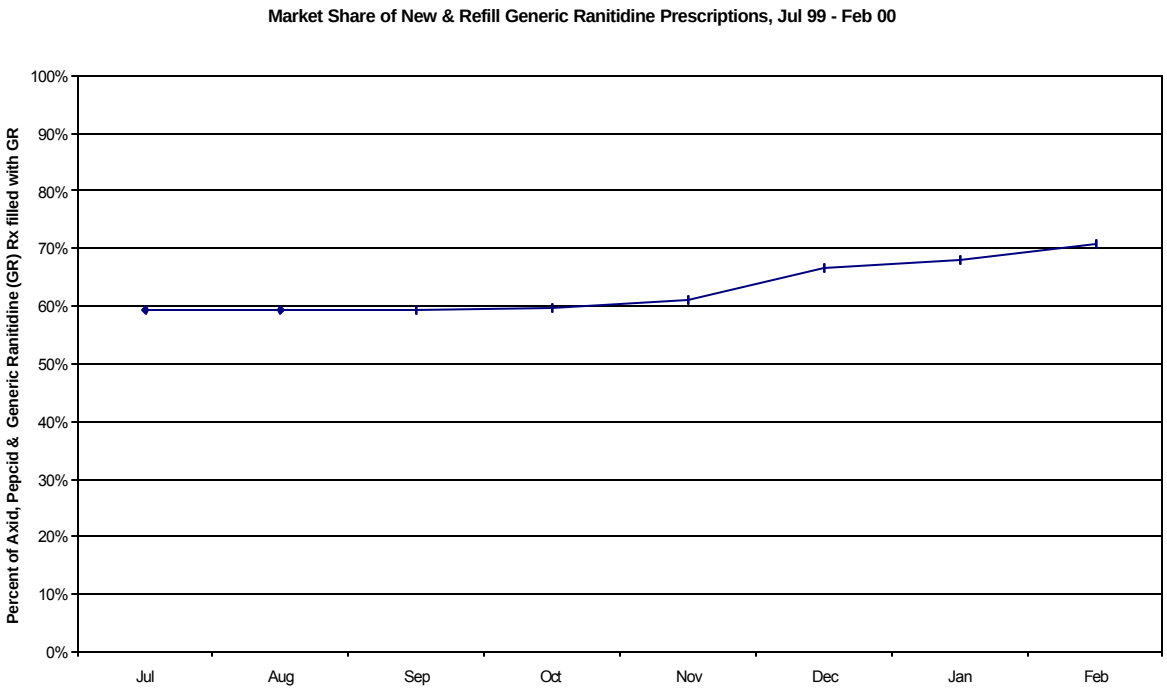
4. H2 Blockers

Generic ranitidine was designated as preferred in NMOP in August 99. Axid (nizatidine) and Pepcid (famotidine) are non-preferred. Implementation began in December, 1999.

Table 4: Prescriptions for Non-Preferred H2 Blockers in NMOP, Dec 99 – Feb 00[1]				
Month	Dec	Jan	Feb	**Dec 99-Feb 00**
New Rxs Received	213	240	234	**687**
Prescriber Contacts	182	228	210	**620**
Switches	117	169	117	**403**
Switch rate[2]	55%	70%	50%	**59%**

1 From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 01 December 1999 through 29 February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic ranitidine.

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Dec 99	Jan 00	Feb 00	**Dec 99-Feb 00**
Monthly Cost avoidance	$10,167	$15,285	$16,907	**$42,359**

*Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the prescriptions had not been switched. The figure for "would-have-been" expenditures is derived by multiplying the mean percentage of market share (by prescription; both new and refill) during Jul 99-Nov 99 for each drug by the total number of new and refill prescriptions in each month for all non-preferred and preferred drugs, and then multiplying this figure by the average cost per prescription for each drug, and summing for all non-preferred and preferred drugs.

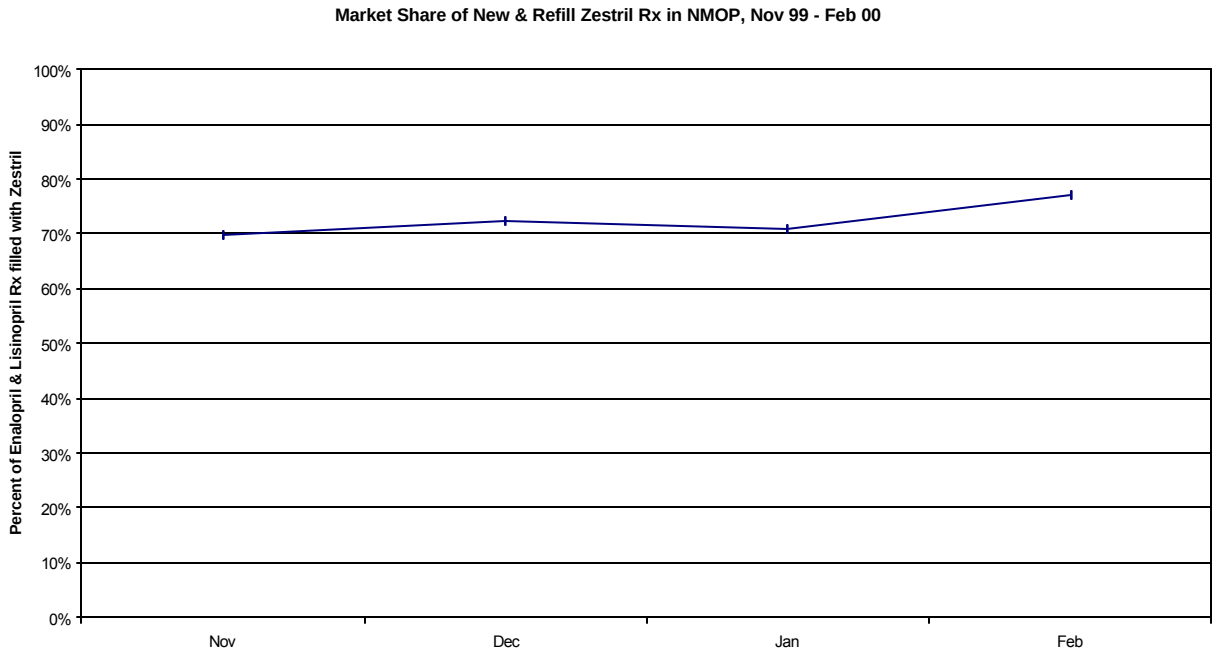
5. Enalapril

Zestril (lisinopril) generic was designated as preferred in NMOP in August 99. Vasotec (enalopril) was designated non-preferred. Implementation began in February 2000.

Table 5: Prescriptions for enalapril in NMOP, Feb 00[1]	
Month	Feb 00
New Rxs Received	265
Prescriber Contacts	239
Switches	146
Switch rate[2]	55%

1 From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to Zestril

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Feb 00
Monthly Cost avoidance	$12,069

*Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the prescriptions had not been switched. The figure for "would-have-been" expenditures is derived by multiplying the mean percentage of market share (by prescription; both new and refill) during Nov 99 – Jan 00 for each drug by the total number of new and refill prescriptions in each month for all non-preferred and preferred drugs, and then multiplying this figure by the average cost per prescription for each drug, and summing for all non-preferred and preferred drugs.

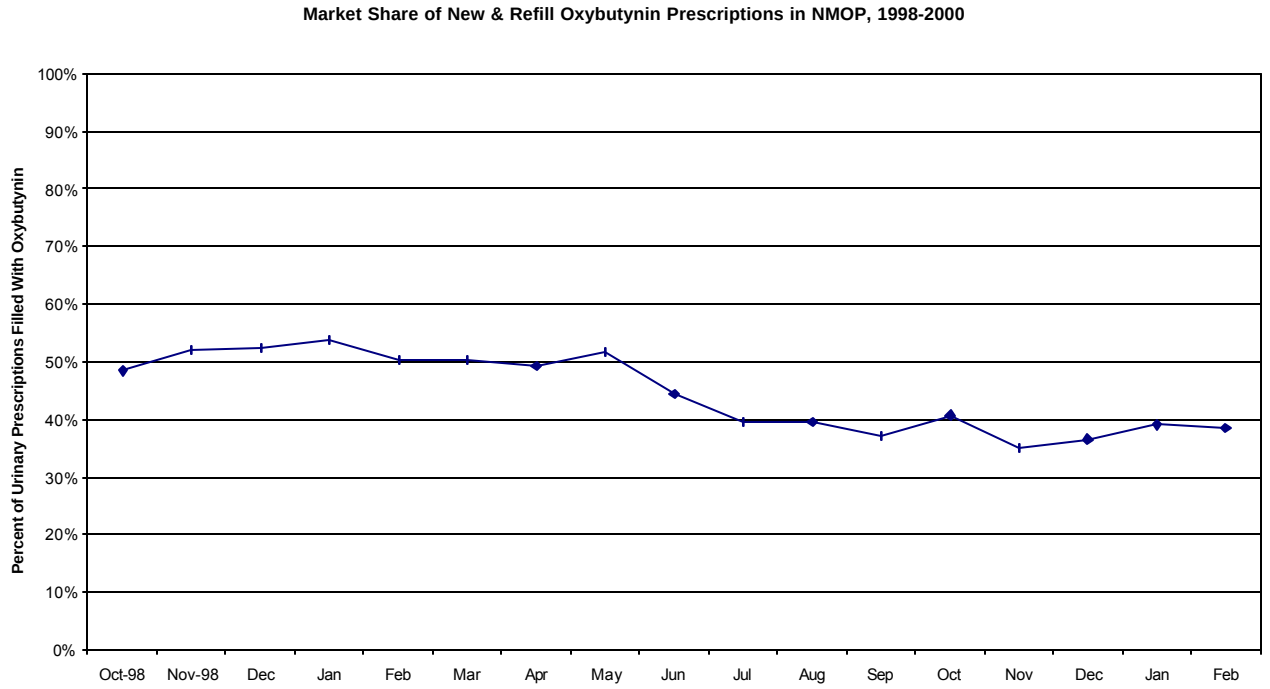
6. Urinary Agents

In November 1998, the DOD P & T Committee selected oxybutynin generic as the preferred urinary agent. Detrol and Ditropan XL are non-preferred.

Table 6: Prescriptions for Non-Preferred Urinary Drugs in NMOP, Jun 99 – Feb 00[1]										
Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	**Jun 99 – Feb 00**
New Rxs Received	224	183	270	271	308	325	363	270	272	**2486**
Prescriber Contacts	195	158	233	236	270	256	331	248	247	**2174**
Switches	80	40	76	69	95	88	105	83	100	**736**
Switch rate[2]	36%	22%	28%	25%	31%	27%	29%	31%	37%	**30%**

1. From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 29 May 1999 through 29 February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic oxybutynin

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Jun 99	Jul 99	Aug 99	Sep 99	Oct 99	Nov 99	Dec 99	Jan 00	Feb 00	**Jun 99 – Feb 00**
Monthly Cost Avoidance	$7,735	$4,355	$6,823	$6,575	$8,769	$8,414	$10,271	$7,953	$10,075	**$70,970**

Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the stated prescriptions had not been switched. Derived by multiplying the number of reported prescriptions switched for each target drug times the difference in average cost per prescription (target drug – oxybutynin). [Note: this is a different methodology than used for other drugs and is due to difficulties in establishing a baseline percentage of market share for each of these drugs and uncertainty as to the validity of carrying percentages through to subsequent months.]

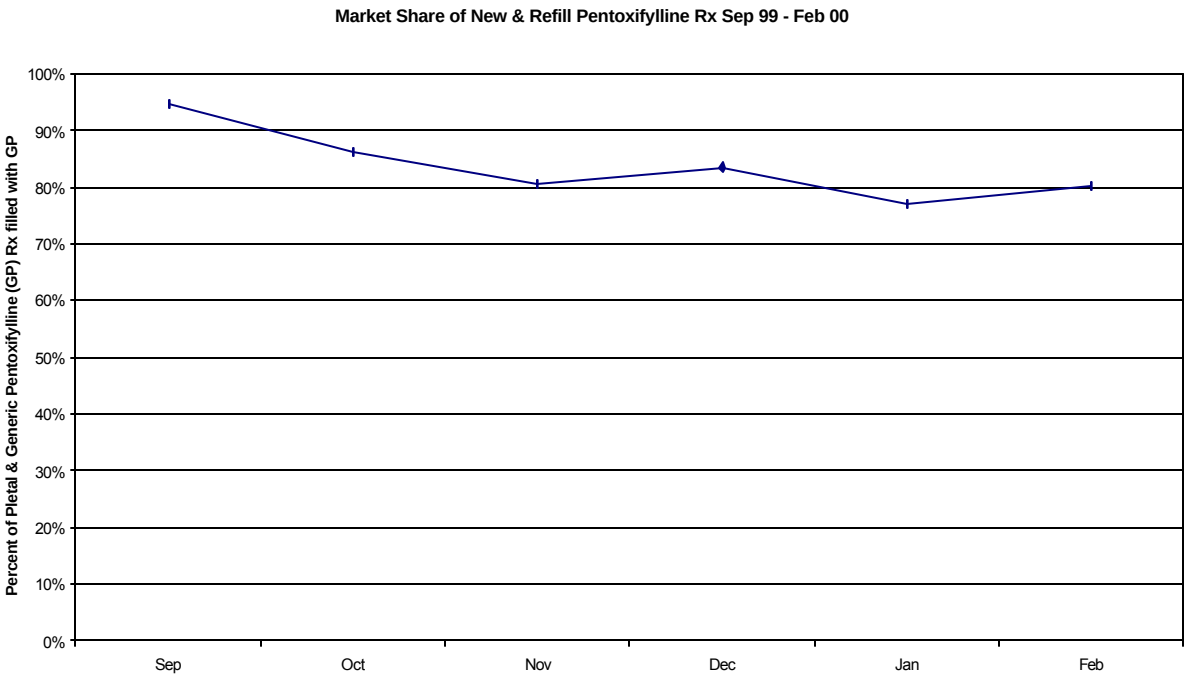
7. Cilostazol

Pentoxifylline generic was designated as preferred in NMOP in August 99. Pletal (cilostazol) was designated non-preferred. Implementation began in February 2000.

Table 7: Prescriptions for Non-Preferred Claudication Agents in NMOP, Feb 00[1]	
Month	Feb 00
New Rxs Received	23
Prescriber Contacts	21
Switches	5
Switch rate[2]	21%

1 From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic pentoxifylline

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	**Sep 99-Feb 00**
Monthly Cost avoidance	$466

***** Monthly cost avoidance calculated by subtracting current expenditures from expenditures that would have occurred if the stated prescriptions had not been switched. Derived by multiplying the number of reported prescriptions switched for each target drug times the difference in average cost per prescription (target drug – pentoxifylline). [Note: this is a different methodology than used for other drugs and is due to difficulties in establishing a baseline percentage of market share for each of these drugs and uncertainty as to the validity of carrying percentages through to subsequent months.]

8. Herpes Antivirals

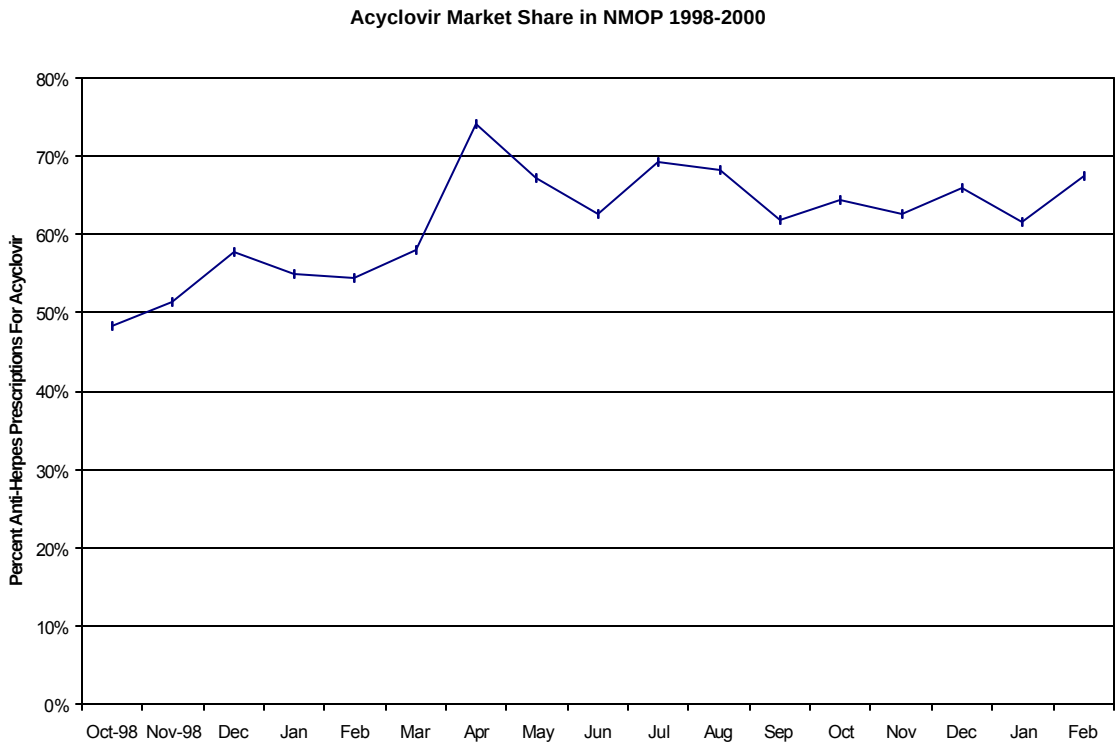
Generic acyclovir is the preferred herpes antiviral. Famciclovir (Famvir; SmithKline Beecham) and valacyclovir (Valtrex; Glaxo) are non-preferred agents. Famciclovir was selected as a non-preferred agent in Nov 98 and valacyclovir in Feb 99.

Table 5: Prescriptions For Non-Preferred Herpes Antivirals in NMOP, Jun 99 – Feb 00[1]

Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Jun 99 –Feb 00
New Rxs Received	77	52	51	44	60	62	70	70	76	**562**
Prescriber Contacts	68	44	39	30	41	46	57	59	50	**434**
Switches	28	14	21	21	15	17	17	29	25	**187**
Switch rate[2]	36%	27%	54%	41%	25%	27%	24%	41%	33%	**33%**

1. From Merck-Medco reports "NMOP Switch Report", "DoD Target Drug Report", and "DoD Prescription Volume Report" covering period from 29 May 1999 through 29 February 2000.
2. Percentage of new prescriptions received for non-preferred drugs that were switched to generic acyclovir.

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance*

Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Jun99 –Feb00
Monthly Cost Avoidance	$666	$302	$635	$410	$409	$406	$406	$679	$608	**$4521**

* See section following for an explanation of the assumptions underlying this estimate

Explanation of Methodology: Cost Avoidance Estimate for Herpes Antivirals

Assumptions needed to be made in order to estimate cost avoidance with this set of drugs given the level of available data. This is because dosing regimens and quantities dispensed per prescription vary widely for herpes antivirals according to 1) the disease being treated (*h. zoster*, *h simplex*) and 2) the reason for use (treatment, chronic suppression). Treatment of *h. simplex* costs less than treatment of *h. zoster*. There is also a difference in cost between famciclovir and valacyclovir for each regimen.

Regimen Costs of Herpes Antivirals in Switch Program		
Drug	**Dose**	**Cost**
Famciclovir	125 mg bid x 5 days (simplex) 500 mg q8h x 7 days (zoster)	$11.20 (simplex) $47.04 (zoster)
Valacyclovir	500 mg bid x 5 days (simplex) 1 gm tid x 7 days (zoster)	$20.30 (simplex) $30.03 (zoster)
Generic acyclovir	200 mg 5xd for 10 days (simplex) 800 mg 5xd for 7-10 days (zoster)	$1.00 (simplex) $12.00 (zoster)

Comparison of Cost Avoidance

Drug switched to acyclovir	**Cost avoidance if prescription written to treat *h. zoster***	**Cost avoidance if prescription written to treat *h. simplex***
Famciclovir	$35.04	$10.20
Valacyclovir	$18.03	$19.30

To estimate cost avoidance, we made the following assumptions:

- All prescriptions switched from valacyclovir to generic acyclovir were for the treatment of h. *simplex* (resulted in a cost avoidance of $19.30 per switch)
- All prescriptions switched from famciclovir to generic acyclovir were for the treatment of h. *zoster* (resulted in a cost avoidance of $35.04 per switch)
- Refills were not authorized on any famciclovir or valacyclovir prescriptions

For example, in the month of June, 8 of the 28 switches were for famciclovir prescriptions and 20 of the 28 were for valacyclovir prescriptions. To maximize estimated cost avoidance, it was assumed that all famciclovir switches were prescriptions written to treat h. *zoster* (8 switches @ $35.04 each = $280) and all Valrex switches were prescriptions written to treat h. *simplex* (20 switches @ $19.30 each = $386). Total cost avoidance in June is estimated at $666 ($280 + $386).

This estimate of monthly cost avoidance assumes maximal cost savings in the treatment of h. *simplex* and h. *zoster*.

May 00 NMOP Preferred/Non-Preferred Pairs Program Report:
Summary of Switch Rates and Estimated Cost Avoidances Jun 99 – Feb 00

Non-Preferred Drug	Preferred Drug	Switch Rate[1]	Estimated Cost Avoidance[1]	Total Number of Attempted Provider Contacts[2]	Estimated Cost Avoidance per Attempted Provider Contact[3]	Annualized Estimated Cost Avoidance
Cardizem CD Dilacor XR, Diltia XT, Diltiazem XR	**Tiazac**	69%	$273,599	3647	$75	$364,799
Procardia XL	**Adalat CC**	56%	$241,638	1415	$171	$322,184
Lodine XL, Relafen, Voltaren XR, DayPro, Naprelan	**Generic NSAIDs**	34%	$342,206	4128	$83	$456,275
Axid, Pepcid	**Generic ranitidine**	59%	$42,359	687	$62	$169,436
Vasotec	**Zestril**	55%	$12,069	265	$46	$144,828
Ditropan XL, Detrol	**Generic oxybutynin**	30%	$70,970	2486	$29	$94,627
Pletal	**Generic pentoxi-fylline**	21%	$466	23	$20	$5592
Valacyclovir, Famciclovir	**Generic acyclovir**	33%	$4521	562	$8	$6028
	Total	**$987,362**	**13,187**	**$75**	**$1,563,769**	

1. From May 2000 NMOP Preferred/Non-Preferred Pairs Program Report (Tables 1-8)
2. Assumes that each new prescription received for a non-preferred drug results in one attempted provider contact
3. Calculated as the total cost avoidance Jun 99 – Feb 00 divided by the total number of attempted provider contacts made for non-preferred drugs in this class during the same period

Appendix B: Quantity Limits for Selected High-Cost Topicals in the NMOP and Retail Pharmacy Network

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Imiquimod (Aldara)	**none**	**Retail:** 1 box of 12 single-use packets per 30 days (12 units) **Mail order:** 3 boxes of 12 single-use packets per 90 days (36 units)	Immune response modifier with an unknown mechanism of action, used to treat external genital and peri-anal warts. The manufacturer recommends dosing three times weekly, prior to sleep, to be left on for 6-10 hours, until total clearance or for maximum of 16 weeks. The product is supplied in boxes containing 12 single-use packets. AWP Cost: $10.40 per packet
Calcipotriene (Dovonex)		**Retail:** 300 gm or mL per 30 days* **Mail order:** 900 gm or mL per 90 days*	Synthetic vitamin D3 derivative used to treat moderate plaque psoriasis. The product is supplied as 0.005% ointment, cream, and solution in 30-, 60-, and 100-gm tubes and 60-mL bottle. AWP Cost: $1.55 per gm or mL.
Alitretinoin (Panretin)		**Retail:** 60 gm (1 tube) per 30 days **Mail order:** 180 gm (3 tubes) per 90 days	Retinoic acid derivative used to treat cutaneous lesions in patients with AIDs-related Kaposi's sarcoma. Directions are to apply sufficient gel to lesions twice daily and may gradually increase to 3-4 times daily, depending on tolerance. There is no established maximum dose. The product is supplied as a 0.1% 60-gm tube. According to the manufacturer, Ligand Pharmaceuticals, a 60-gm tube would be considered a 1 to 2-month supply based on surface area. AWP cost: $40.00 per gm
Becaplermin (Regranex)		**Retail:** 15 gm per 30 days* **Mail order:** 45 gm per 90 days*	Recombinant platelet-derived growth factor (rhPDGF) used to treat diabetic ulcers with an adequate blood supply. The amount applied once daily varies depending on the size of the ulcer area. The package labeling has a detailed calculation table. Dosage should be recalculated weekly or biweekly as the ulcer area changes. The product is supplied as a 0.01% gel in 2-, 7.5-, and 15-gm tubs. A 15-gm tube will express 60 cm of gel, which is adequate to treat one 7 cm^2 ulcer for 34 days. AWP cost: $27.50 per gm
Tazarotene (Tazorac)		**Retail:** 100 gm per 30 days* **Mail order:** 300 gm per 90 days*	Retinoid prodrug indicated for treatment of facial acne vulgaris of mild to moderate severity. It is also used to treat stable plaque psoriasis of up to 20% body surface area involvement. The product is supplied as 0.1% or 0.05% gel in 30- and 100-gm tubes. When treating facial acne, one 30-gm tube would last approximately 2 to 3 months. In treating psoriasis, one 100-gm tube would last approximately 1 month. There is no established maximum dose. AWP cost: $2.12 per gm

***Any combination of package sizes up to the maximum amount listed.**

Appendix C: Review of Ophthalmic Glaucoma Agents and BCF Recommendations—CDR Matt Nutaitis

Ophthalmic Glaucoma Agents Currently on the BCF

1. Timolol Ophthalmic Solution
   [Does not include timolol maleate gel (Timoptic XE)]
2. Betaxolol Ophthalmic Suspension (Betoptic; Alcon)
3. Pilocarpine Ophthalmic Gel
4. Pilocarpine Ophthalmic Solution
5. Dorzolamide Ophthalmic Solution (Trusopt; Merck)

Recommendations for BCF Changes

Removal of:

Betaxolol Ophthalmic Suspension
Pilocarpine Ophthalmic Gel
Dorzolamide Ophthalmic Solution

Addition of:

Brimonidine Ophthalmic Solution (Alphagan; Allergan)

Discussion

The review of the topical glaucoma agents and their presence on the BCF included a multi-phased decision process. The current BCF drugs were identified, input from a glaucoma specialist from each of the three services was solicited, and an adjustment to the BCF drugs was recommended.

The advisory group for this BCF decision was comprised of a representative from each of the services. The Army was represented by MAJ Brian Cavallero. LTC Flynn provided input for the Air Force, and CDR Diane Lundy supplied an opinion for the Navy.

Recommended BCF topical glaucoma agents: timolol ophthalmic solution, brimonidine ophthalmic solution, pilocarpine ophthalmic solution

- Due to pricing available through a DoD/VA mandatory source contract (awarded to Alcon Labs), timolol is the most cost-effective of the topical ophthalmic beta-blockers. The use of beta-blockers is common in the first line treatment of glaucoma, and thus, reason to include a beta-blocker on the BCF. The timolol products have a long track record of safety and efficacy, and are popular choices by ophthalmologists in the treatment of glaucoma patients. Retention of timolol ophthalmic solution on the BCF is recommended.

  The continued exception of timolol maleate gel (Timoptic XE, generics) from the BCF listing for timolol solution is recommended. Although this extended-release product is now generically available, it is still at least twice as costly as timolol solution on a daily basis. Local MTFs may decide to add timolol maleate gel to their formularies if they choose to do so. There is a DoD/VA mandatory source contract in effect for timolol maleate gel (awarded to Merck &

Co); however, this contract does not mandate inclusion of timolol ophthalmic gel on the BCF. Usage of timolol is about 56% timolol solution and 44% timolol maleate gel in terms of bottles purchased.

- Brimonidine (Alphagan; Allergan) is a safe and efficacious first line medication to treat glaucoma. In the Alpha Agonist class of anti-glaucoma medications, brimonidine is the least expensive, least allergenic, and is dosed as a BID medication, which assists in patient compliance and satisfaction. This group of medication also has a unique role in the prophylaxis of intraocular pressure spikes, a known complication of YAG laser capsulotomy. Its addition as a BCF drug was unanimous.

- Finally, continued inclusion of pilocarpine solution is recommended. It is inexpensive, efficacious and unique. It is used to treat acute angle closure and to prepare the eye for laser iridotomy procedures.

The recommendations for removal from the BCF are: dorzolamide ophthalmic solution (Trusopt; Merck), betaxolol ophthalmic suspension (Betoptic; Alcon), and pilocarpine ophthalmic gel.

- Clinically, dorzolamide is a second line medication. Brief stinging after the drop application influences patient compliance. The combination of expense and efficacy guided the decision to allow individual hospital formulary committees to consider this as a formulary drug, but not include it on the BCF.

- Betaxolol ophthalmic suspension has a smaller clinical role with the advent of multiple new anti-glaucoma agents. Removal from the BCF with local formulary consideration is recommended.

- Pilocarpine (Pilogel) ophthalmic gel has a very limited clinical role and also should be removed from the BCF.

Also considered for the BCF but not recommended for BCF addition at this time: latanoprost ophthalmic solution (Xalatan; Pharmacia).

- Latanoprost is effective and safe. However, latanoprost costs more than other agents and is not FDA-approved as a first line agent for glaucoma. Also, addition of a 4^{th} agent to treat glaucoma to the BCF was not felt to be necessary. The consultants agreed that local commands should be allowed to add latanoprost to their formularies if they so desire.

Appendix D: Oral Contraceptive Agents (OCPs)[1]

Monophasic OCPs with 20mcg ethinyl estradiol (EE)

Brand Name	Estrogen	Progestin	Cost/Cycle[2] (May 00 DAPA price)	BCF Item?
Alesse-28 Levlite-28	EE 20	0.10mg levonorgestrel	$6.00 $5.99	No
Loestrin FE 1/20	EE 20	1.00mg norethindrone acetate	$2.00 (28 day)	No

Monophasic OCPs with 30mcg EE

Levlen Levora Nordette	EE 30	0.15mg levonorgestrel	$1.28 $6.00 $6.00	No
Lo/Ovral Low-Ogestrel	**EE 30**	**0.30mg norgestrel**	**$8.00 $8.00**	**Yes**
Loestrin-FE 1.5/30	**EE 30**	**1.50mg norethindrone acetate**	**$2.00 (28 day)**	**Yes (added 11 May 00)**
Desogen Ortho-Cept Apri	EE 30	0.15mg desogestrel	$12.06 $16.57 not listed[3]	No

Monophasic OCPs with 35mcg EE

Brevicon Modicon Necon	EE 35	0.50mg norethindrone	$3.38 $16.76 $3.75	No
Demulen Zovia	**EE 35**	**1.00mg ethynodiol diacetate**	**$3.89 $3.75**	**Yes (added 11 May 00)**
Necon Norinyl Ortho-Novum	**EE 35**	**1.00mg norethindrone**	**$3.75 $3.81[4] $13.59**	**Yes**
Ovcon	EE 35	0.40mg norethindrone	$15.83	No
Ortho-Cyclen	EE 35	0.25mg norgestimate	$16.19	No

Biphasic OCPs

Mircette	EE 20/0.01mg	0.15mg desogestrel	$12.06	No
Jenest Necon 10/11 Ortho-Novum 10/11	EE 35	0.5mg/1.00mg norethindrone	$11.25 $3.75 $15.98	No

Triphasic OCPs

Tri-Norinyl	EE 35	0.5/1/0.5mg norethindrone	$3.81	No
Ortho-Novum 7/7/7	**EE 35**	**0.5/0.75/1mg norethindrone**	**$15.78[5]**	**Yes**
Ortho Tri-Cyclen	EE 35	0.18/0.215/0.25mg norgestimate	$16.35	No
Estrostep-FE	EE 20/30/35	1.00mg norethindrone acetate	$2.00	No
Trilevlen Triphasil Trivora	**EE 30/40/30**	**0.05/0.075/0.125mg levonorgestrel**	**$1.28 $6.00 $13.11**	**Yes**

Progestin-Only OCPs

Micronor Nor-Q.D.		**0.35mg norethindrone**	**$18.82 $6.30**	**Yes (added 11 May 00)**
Ovrette		0.075mg norgestrel	$15.63	No

1. OCPs with 50 mcg EE or mestranol not listed due to infrequency of use (about 2.5% of all cycles purchased)
2. DAPA prices listed are for 28-day packs, which represent approximately 95% of total use compared to 21-day packs. Prices do not reflect bulk discounts.
3. Recently approved. Per the manufacturer, FSS price is approximately $10.20 per cycle; DAPA price not yet listed
4. Norinyl 1/35 28-day packs available through the depot at approximately $5.30 per cycle, including the depot surcharge. This is higher than the $3.81 price through the prime vendor.
5. Ortho-Novum 7/7/7 (clinic packs) available through the depot at approximately $5.56 per cycle, including the depot surcharge. This is considerably lower than the $15.78 price through the prime vendor.

Appendix E: Formulary Changes

I. BCF Changes

A. *Addition of the following:*

1. Brimonidine Ophthalmic Solution (Alphagan; Allergan)—see Paragraph 5C7
2. Metronidazole vaginal gel (Metrogel Vaginal; 3M Pharmaceuticals)—see Paragraph 5C8
3. Ethinyl estradiol 30 mcg/1.5 mg norethindrone (Loestrin FE 1.5/30)—see Paragraph 5C11b
4. Ethinyl estradiol 35 mcg/1 mg ethynodiol diacetate (e.g., Demulen, Zovia)—see Paragraph 5C11c
5. 0.35 mg norethindrone (e.g., Micronor, Nor-Q.D.)—see Paragraph 5C11f
6. Extended release morphine (MS Contin or its AB-rated generic only) 15-, 30-, and 60-mg tablets [The BCF requirement does not include 100- or 200-mg tablets of MS Contin and does not include other extended release morphine products (e.g., Oramorph SR or Kadian)]. (see Paragraph 5C12)

B. *Removal of the following:*

1. Betaxolol Ophthalmic Suspension—see Paragraph 5C7
2. Dorzolamide Ophthalmic Solution—see Paragraph 5C7
3. Pilocarpine Ophthalmic Gel—see Paragraph 5C7

C. *Clarification*—The BCF listing for "oxycodone 5 mg /acetaminophen 325 and 500 mg" was clarified to specify that MTFs must have oxycodone/acetaminophen in the 5/325 and 5/500 mg strengths on their formularies. MTFs are not required to have the 2.5/325, 7.5/500, and 10/650 strengths on their formularies. (See Paragraph 5C9.)

II. NMOP Formulary Changes

A. *Added to the NMOP Formulary* (see Paragraph 5C1):

1. Levetiracetam tablets (Keppra; UCB Pharma)
2. Ciclopirox topical solution (Penlac Nail Lacquer; Dermik/Aventis)
3. Nedocromil sodium ophthalmic solution, 2% (Alocril; Allergan)
4. Cevimeline HCl capsules (Evoxac; Snowbrand Pharma)
5. Alosetron tablets (Lotronex; Glaxo)—added to the NMOP formulary for female patients only
6. Rivastigmine capsules (Exelon; Novartis)
7. Sotalol HCl (BetapaceAF™; Berlex)

B. *Excluded from the NMOP Formulary*

1. Dofetilide (Tikosyn; Pfizer) was excluded from the NMOP formulary and will not be available through the NMOP. (See Paragraph 5C2.)
2. Alosetron (Lotronex; Glaxo) was excluded from the NMOP formulary if prescribed for male patients. (See Paragraph 5C1.)

C. *Clarification*—The committee clarified the current listing for antihemophilic factors on the NMOP Covered Injectables List to read " Antihemophilic Factors (including Factor VII, Factor VIII, Factor IX, Factor IX Complex, and Anti-Inhibitor Factor Complex)." (See Paragraph 5C3.)

D. *Changes to the NMOP Preferred Drug Program*

1. Deletion of non-preferred/preferred pair for nitroglycerin patches (see Paragraph 4A2)
2. Change to calling program for herpes antivirals (see Paragraph 4C2)

III. *Quantity Limit Changes (NMOP and retail network)*

A. Quantity limits finalized and approved by committee, will be posted on the PEC website (see Paragraph 4A1).
B. Quantity limits for five high-cost topicals established (see Paragraph 4D and Appendix B).

IV. *Changes to the Prior Authorization Program (NMOP and retail network)*

A. The committee approved prior authorization criteria for the NMOP and retail network for terbinafine (Lamisil) and itraconazole (Sporanox) for treatment of onychomycosis (see Paragraph 4I).
B. The committee decided to revise prior authorization forms to include education for providers (see Paragraph 4K).

Appendix F: Reports Due to the Committee

I. *NMOP Preferred Drug Program Standing Report* (see Paragraph 4C1) — CDR Mark Brouker (PEC). Interim report due to co-chairs by 17 Jul 00, full report to committee at the next meeting.

II. *Report on Feasibility of Proposal Concerning Antivirals in the NMOP Preferred Drug Program* (see Paragraph 4C2—Mark Petruzzi (Merck-Medco). Report due to co-chairs by 17 Jul 00.

III. *Subcommittee Report on Quantity Limits for Topicals* (see Paragraph 4D)—Subcommittee members: Bill Hudson (chair); MAJ George Jones; MAJ Mickey Bellemin; Ray Nan Berry (Foundation Health); Kirby Davis (Anthem Alliance); William Hudson (Humana); Gene Lakey (TriWest); and Ron McDonald (Sierra Military Health Services). Interim report due to co-chairs by 17 Jul 00.

IV. *Subcommittee Report on Cost-Efficiency of Prior Authorizations in the NMOP* (see Paragraph 4H)—Subcommittee members to be named. Report due to co-chairs by 17 Jul 00.

Department of Defense
Pharmacoeconomic Center

1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE 24 February 2000

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 24 February 2000, at the Naval Amphibious Base Little Creek, Portsmouth, VA.

2. MEMBERS PRESENT:

CDR Terrance Egland, MC	Co-chairman
COL Daniel D. Remund, MS	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
CDR Matt Nutaitis, MC	Navy
LCDR Kevin Cook, MSC	Navy
COL (select) Bill Sykora, MC	Air Force
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
LCDR Pamela Stewart Kuhn	Coast Guard (alternate)
Ronald L. Mosier	Department of Veterans Affairs (alternate)
LTC Greg Russie, BSC	Joint Readiness Clinical Advisory Board (alternate)
LTC Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services

Daniele Doyle was absent.

3. OTHERS PRESENT:

CAPT Charlie Hostettler, MSC	DoD Pharmacy Program Director, TMA
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Bob Wilkens, MSC	Navy Pharmacy Specialty Leader
CAPT (select) Betsy Nolan, MSC	TRICARE, Mid-Atlantic Region
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center (PEC)
Howard Altschwager	Deputy General Counsel, TMA
David Chicoine	Uniformed Services Family Health Plans (USFHP)
Tom Kellenberger	Merck-Medco
Mark Petruzzi	Merck-Medco
Shana Trice	DoD Pharmacoeconomic Center (PEC)
Paul Vasquez	Defense Supply Center Philadelphia (DSCP)

4. ADMINISTRATIVE ISSUES:

A. The minutes from the last meeting were accepted as written. In response to a question from MAJ Bellemin, the committee confirmed that zolpidem (Ambien®) is subject to the standard quantity limit of a 30-day supply for controlled substances.

5. OLD BUSINESS

A. Review of Interim Decisions

1. *Advances in Medical Practice (AMP) Program*—Voting members of the DoD P&T Committee met via teleconference on 26 Jan 00 to recommend drugs for coverage by the AMP program. The minutes for the interim meeting are at Appendix A. (NOTE: The minutes for the interim meeting were not previously posted on the PEC website because it would have been premature to announce the drug recommendations before AMP program officials had a chance to review them.) At the request of AMP program officials, the P&T committee co-chairs subsequently recommended more drugs for coverage by the AMP program. The consolidated list of all drugs recommended by the DoD P&T Committee for coverage under the AMP program is at Appendix B. MTFs will be informed when AMP officials, TMA officials, and service resource management officers have approved the list of drugs and finalized procedures for reimbursing MTFs for expenditures on drugs covered by the AMP program.

2. *Additions to BCF due to Program Budget Decision (PBD) No. 41*—The DoD P&T Committee met via teleconference on 26 Jan 00 to add drugs to the Basic Core Formulary (BCF) in response to additional funding for MTF pharmacies provided by the PBD No. 41. The minutes for this meeting were previously posted on the PEC website. The committee added the following drugs to the BCF:

    - metformin
    - tamoxifen

- alendronate
- citalopram
- fluoxetine
- paroxetine
- sertraline
- sumatriptan autoinjector

The committee also modified the BCF to stipulate that all MTFs must have at least one agent from each of the following classes on their formularies:

- oral serotonin 5-HT_1 receptor agonists (naratriptan, rizatriptan, sumatriptan, zolmitriptan)
- low molecular weight heparins/heparinoids (ardeparin, dalteparin, danaparoid, enoxaparin)
- leukotriene antagonists (montelukast, zafirlukast, zileuton)
- second-generation antihistamines (cetirizine, fexofenadine, loratadine)

The PEC will furnish information to MTFs to assist them in selecting agents for their formularies.

B. National Mail Order Pharmacy (NMOP) Preferred Drug Program

When the NMOP receives a new prescription for a non-preferred drug, the NMOP contractor, Merck Medco, attempts to contact the prescriber to request a switch to a preferred drug if clinically appropriate. CDR Brouker reported the switch rates and estimated cost avoidance for non-preferred/preferred drug pairs in the NMOP (see Appendix C). MAJ Bellemin reported that Merck-Medco started calling prescribers on 1 Dec 99 regarding the new non-preferred/preferred drug pairs that were approved at the Aug 99 meeting. These drug pairs are: famotidine/ranitidine (Geneva brand); nizatidine/ranitidine (Geneva brand); nitroglycerin patches other than Nitro-Dur®/Nitro-Dur®; and enalapril/lisinopril (Zestril®). Data for the new non-preferred/preferred drug pairs will be reported at the next meeting.

C. Quantity Limits

1. The PEC and the Defense Supply Center Philadelphia (DSCP) continue to check the quantity limits that Merck Medco actually applies in the NMOP to ensure that they match the official quantity limits that are listed on the PEC website at http://www.pec.ha.osd.mil/NMOP/qtylimit.htm.

2. *Report of the subcommittee on quantity limits for topicals*—Bill Hudson (Humana) and MAJ George Jones recommended quantity limits for five high-cost topicals [imiquimod (Aldara); calcipotriene (Dovonex); altitretinoin (Panretin); becaplermin (Regranex); and tazarotene (Tazorac)]. The proposed quantity limits for most of the agents were expressed in terms of the maximum number of containers of any size that would be dispensed in a given time period (30 or 90 days). Several committee members expressed concern that this might be overly restrictive and supported the concept of expressing the quantity limits in

terms of the maximum number of grams or milliliters dispensed in a given time period, with the maximum quantity set to allow for the vast majority of all use. The P&T Committee did not approve the recommended quantity limits for the topical agents listed above. The P&T Committee asked the subcommittee to provide additional information concerning the frequency distribution of quantities dispensed for these agents in the retail networks and the NMOP in order to more accurately establish 1) if any quantity limitation is necessary, and 2) if so, what a reasonable limit would be.

3. *Change in quantity limit for azithromycin*—The committee approved a recommendation by Gene Lakey (Triwest) to increase the current 6-tablet per 30 day quantity limit for azithromycin (Zithromax®) 250-mg tablets to 10 tablets per 30 days. This change in the quantity limits is necessary to accommodate dosing requirements for older children for the treatment of pharyngitis/tonsillitis.

D. *Cost-efficiency of prior authorizations in the NMOP*—MAJ Bellemin reported on the prior authorization programs for sildenafil, etanercept, rofecoxib, and celecoxib in the NMOP.

1. *Sildenafil*—Merck Medco performed 7696 prior authorizations (4865 approved and 2831 denied) at a cost of $307,840 from September 99 through December 99. Based on utilization data from June through December 1999 and the current government price for sildenafil, it is estimated that prior authorization of sildenafil will provide a $47,280 cost avoidance during the next 12-month period.

2. *Etanercept*—Merck Medco performed 161 prior authorizations (152 approved and 9 denied) at a cost of $6440 from August 99 through December 99. Based on utilization data from June through December 1999 and the current government price for etanercept, it is estimated that prior authorization of etanercept will provide a $64,084 cost avoidance during the next 12-month period.

3. *COX-2 inhibitors (celecoxib, rofecoxib)*— Merck-Medco processed 9695 prescriptions for COX-2 inhibitors from August 99 through December 99. The automated prior authorization process approved 5574 of the prescriptions; 4121 required prescriber contact. Of these, 3100 were approved and 1021 were denied at a cost of $164,840. Based on COX-2 utilization data from June through December 1999 and the current government price for these agents, it is estimated that DoD will realize a $908,026 cost avoidance during the next 12-month period.

Several members commented that the cost avoidance is underestimated because the mere existence of the prior authorization program may cause physicians to write fewer prescriptions for a drug (usually referred to as the “sentinel effect”). Other members commented that the cost avoidance is overestimated because prescriptions that are initially denied are sometimes filled when resubmitted because the prescriber provides additional information that satisfies the prior authorization criteria. Cost avoidance was also overestimated because the analysis did not account for the cost of NSAIDs or other drugs that were prescribed when the prior authorization process denied the COX-2 prescription. The PEC staff will work with MAJ Bellemin to improve the validity of the cost avoidance estimates. MAJ Bellemin will continue to report on this subject as a standing report at each meeting. The report for the next meeting is due to the co-chairs by 11 Apr 00.

E. *Prior authorization for terbinafine*—The committee co-chairs finalized the prior authorization criteria for terbinafine in January, but TMA directed that implementation be held in abeyance until TMA clarified the definition of cosmetic vs. non-cosmetic use of terbinafine and its status as a covered benefit under TRICARE. CAPT Hostettler informed the committee during the meeting that TMA considers treatment of a documented infection to be a covered benefit under TRICARE and that such treatment should not be characterized as cosmetic.

The question of whether the prior authorization should apply only to terbinafine or to both terbinafine and itraconazole was reintroduced. Some committee members thought that prior authorizing only terbinafine might lead to increased use of itraconazole. Arguments favoring prior authorizing only terbinafine included:

- Prior authorization of itraconazole might be cost-inefficient. Itraconazole is used for many indications other than onychomycosis, so the NMOP might incur large prior authorization expenses with little impact on itraconazole usage.
- One MCSC director stated that, in their experience, institution of a prior authorization program focused only at terbinafine did not lead to increased usage of itraconazole.

Paul Vasquez commented that the NMOP might be able to ascertain (as a benefit issue) whether or not these medications were being prescribed for onychomycosis. The government would then incur the prior authorization fee only for prescriptions for treatment of onychomycosis. Mr. Vasquez will investigate this issue and report his findings to a subcommittee consisting of CDR Egland (chair), Paul Vasquez (DSCP), MAJ Bellemin (DSCP), and MAJ Ed Zastawny (PEC). The subcommittee will then develop a prior authorization proposal and present it at the next P&T committee meeting. An interim report is due to co-chairs by 11 Apr 99.

6. NEW BUSINESS

A. Prior Authorizations

1. *Prior authorization criteria and fax forms on the PEC website*—At the last meeting, the committee directed the PEC to post the prior authorization fax forms (instead of the prior authorization criteria) on the PEC website. MTFs and Managed Care Support Contractors (MCSCs) subsequently requested that the criteria be reinstated on the website. The committee approved the request. The PEC will post both the criteria and the fax forms on the website.

2. *Proposal for prior authorization of fertility drugs*—According to the Code of Federal Regulations (CFR) and TRICARE policy, fertility drugs are not a covered benefit when used to assist in non-coital reproduction methods. Some of the MCSCs have prior authorizations in place for fertility medications, but others do not. The NMOP does not have a prior authorization process for fertility agents and is currently filling a large number of prescriptions for these medications. The committee concluded that a prior authorization for fertility drugs should be established in order to comply with TRICARE policy. CAPT Hostettler will submit draft prior authorization criteria for fertility agents to the co-chairs. The co-chairs will finalize the criteria for approval at the May P&T Committee meeting. CDR Egland is the point of contact for this action.

3. *Proposal to modify COX-2 prior authorization criteria*—The committee discussed several proposals by Bill Hudson (Humana) concerning the prior authorization criteria for COX-2 inhibitors in the NMOP and retail network. The committee agreed that there is not enough clinical evidence to justify use of a COX-2 solely on the basis of recent use of a NSAID for the last 40 of 60 days and decided to remove this as a criterion for approval of the PA for COX-2 inhibitors. The committee also agreed to replace the phrase *"situations where the physician indicates that the patient has previously been unable to tolerate therapy with at least two different NSAIDs"* with the phrase *"situations where the physician indicates that the patient has previously failed an adequate trial with at least two different NSAIDs."* The committee made this change with the intent that "failing an adequate trial" would include both failures due to intolerance and failures due to lack of effectiveness at an dose and duration considered by the physician to constitute an adequate trial.

4. *Report of the Growth Hormone subcommittee*—Bill Hudson (Humana) submitted the subcommittee report, which included proposed criteria for prior authorization of growth hormone products. The P&T committee requested additional information before acting on the subcommittee's recommendation. The subcommittee is to finalize the prior authorization criteria and ensure that they clearly address the use of growth hormone products in adults and the off-label uses of growth hormone. The subcommittee should support the prior authorization criteria with a business case analysis that includes historical usage and cost data for growth hormone products in the NMOP and retail network pharmacies. The subcommittee should provide this information to CDR Egland by 11 Apr 00.

5. *Portability of Prior Authorizations*—Bill Hudson (Humana) proposed that prior authorizations should be portable between MCSCs and the NMOP. The committee assigned MAJ Bellemin to investigate the possibility of uploading all prior authorizations completed by the NMOP and the MCSCs to a common site that could be accessed by all parties. The committee also advised MAJ Bellemin, Merck-Medco, and the MCSCs to ensure compatibility of any such process with the Pharmacy Data Transaction Service (PDTS).

B. National pharmaceutical contracts

1. *Contracts awarded since last meeting*—New generic contracts that apply to both DoD and the VA have been awarded by the VA National Acquisition Center for: timolol maleate 0.25% and 0.5% ophthalmic solution, timolol maleate 0.25% and 0.5% ophthalmic gel; levobunolol 0.25% and 0.5% ophthalmic solution; and gemfibrozil 600-mg tablets.

2. *Albuterol inhaler contract*—Warrick is the contracted brand of albuterol inhaler. The FDA issued a Class I recall because some Warrick albuterol inhalers contained no active ingredient. Some MTFs had to purchase non-contracted brands of albuterol inhalers because the Warrick brand was not available. DSCP will take these issues under consideration in regard to renewal of the albuterol inhaler contract. The committee noted that MedWatch forms should be submitted when quality concerns are identified.

3. The PEC uses prime vendor purchase data to quantify the financial impact of national pharmaceutical contracts. COL Remund presented slides showing the cost avoidance associated with the ranitidine (Geneva brand), cimetidine (Sidmak brand), lisinopril (Zestril), diltiazem extended release (Tiazac), and albuterol inhaler (Warrick brand) contracts. These five contracts yielded nearly $6.5 million in cost avoidance for MTFs in FY 99.

4. COL Remund reported on other contracting issues:

   - *Nicotine Patches*— DoD/VA initiative (DoD lead) for 3-step product only. The contract solicitation was issued 15 Feb 00 and closes 15 Mar 00. An award is expected by 28 Apr 00. MTFs that purchase a 3-step nicotine patch will be required to purchase the contracted product. The contract does not stipulate that the nicotine patch will be listed on the BCF.

   - *Felodipine*— The VA will include DoD in the renewal of its Blanket Purchase Agreement (BPA) for felodipine (Plendil). Adding DoD utilization may decrease the BPA price for felodipine.

   - *Estrogen Replacement Therapy*—In light of proposed DAPA price reductions by Wyeth/Ayerst for PremPro and PremPhase, the committee decided not to proceed with a contracting initiative for estrogen replacement products at this time. The committee noted that the possibility should remain open in the future as new products continue to enter the market. The committee agreed that the presence of the incentive agreements should be considered in DoD's future deliberations with the VA. No changes were made to the BCF.

   - *Second Generation Antihistamines*— Pharmaceutical companies are reducing prices or developing incentive pricing agreements in response to the recent change in the BCF that requires each MTF to have at least one second generation antihistamine on its formulary. After the price reductions and/or incentive agreements are finalized, the committee will reassess the advisability of pursuing a national contract for a second generation antihistamine.

     CDR Egland commented that nasal corticosteroids are more cost-effective than second-generation antihistamines for treating symptoms of allergic rhinitis. He specifically referenced a recent review of the treatment of allergic rhinitis in the *American Journal of Managed Care* (Jan 2000 supplement issue).

   - *Furosemide and hydrochlorothiazide*— Pursuing a joint DoD/VA contract (VA lead). These contracts will select specific brands of these drugs for the BCF.

   - *Returned Goods* - Joint DoD/VA initiative (DoD lead). Anticipate that the solicitation for this contract will be issued in April 00.

C. *FY00 National Defense Authorization Act*—CAPT Hostettler and Mr. Altschwager briefed the committee on the ongoing efforts to implement the provisions pertaining to the uniform formulary and the DoD P&T Committee.

D. BCF and NMOP formulary issues:

1. The following drugs that were recently approved by the FDA were added to the NMOP Formulary. None of these drugs were added to the BCF.

    a. Ethinyl estradiol / norethindrone acetate tablets (FemHRT; Parke Davis)
    b. Exemestane tablets (Aromasin; Pharmacia & Upjohn)
    c. Estradiol / norgestimate tablets (Ortho-Prefest; Ortho McNeil)
    d. Aspirin / dipyridamole extended release capsules (Aggrenox; Boehringer-Ingelheim)
    e. Moxifloxacin hydrochloride tablets (Avelox; Bayer)
    f. Gatifloxacin tablets (Tequin; Bristol Myers Squibb)
    g. Oxcarbazepine tablets (Trileptal; Novartis)

2. The following drugs were excluded from the NMOP formulary for the reasons given. Neither of these drugs was added to the BCF. Both drugs will be available through retail network pharmacies.

    a. *Oseltamivir phosphate capsules (Tamiflu; Roche)*—Oseltamivir is a neuraminidase inhibitor for the treatment of uncomplicated acute illness due to influenza A and B virus in adults who have been symptomatic for less than 2 days. Due to the narrow treatment window for this agent, the committee agreed that this drug is not well suited for dispensing through a mail order pharmacy. A similar drug, zanamivir (Relenza; Glaxo), was excluded from the NMOP formulary at the Aug 99 meeting.

    b. *Bexarotene capsules (Targretin; Ligand Pharma)*—Bexarotene is indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy. Bexarotene is Pregnancy Category X and carries a black box warning against use in pregnancy. Package labeling advises that a pregnancy test (for women of child-bearing age) should be obtained within one week prior to starting therapy and repeated at monthly intervals during therapy. In addition, labeling advises that "no more than a one month supply of Targretin® capsules should be given to the patient so that the results of pregnancy testing can be assessed and counseling regarding avoidance of pregnancy and birth defects can be reinforced." In light of this requirement and considering turn-around times for the mail order program, the committee decided that it was not feasible to provide bexarotene through the NMOP.

3. *Pantoprazole (Protonix; Wyeth-Ayerst)* is a new proton pump inhibitor. The national contract for omeprazole requires pantoprazole to be listed as a "non-contracted drug" on the NMOP Formulary. The national contract precludes MTFs from adding pantoprazole to their formularies.

4. *Nasal corticosteroids (BCF)*— At the May 99 meeting, the committee removed beclomethasone 42mcg/spray (Vancenase pockethaler; Schering) from the BCF due to a substantial DAPA price increase and specified that every MTF should have a nasal corticosteroid on its formulary. At the Aug 99 meeting, the committee selected fluticasone nasal spray (Flonase; Glaxo) for the BCF because it was the most cost-effective agent, it is approved for use in patients as young as 4 years old, it is dosed once a day, and allergy/immunology specialists expressed the opinion that fluticasone would be a good selection as a "workhorse" nasal corticosteroid on the BCF. Prime vendor data through the first quarter of FY00 show an increase in use of fluticasone following its selection as the BCF agent and a decrease in use of beclomethasone products following the removal of Vancenase pockethaler as the BCF selection.

   The PEC recently received prescription data from the civilian market that may affect the cost-effectiveness estimates for fluticasone and mometasone. The Aug 99 cost-effectiveness analysis was based on an adult maintenance dose of 2 puffs/day for fluticasone and 4 puffs/day for mometasone (derived from the product labeling). Civilian prescription data indicate that the prescribed puffs per day may be essentially the same for both drugs, which would make fluticasone and mometasone similar in cost-effectiveness. Mometasone was also recently approved for children as young as 3 years of age. The committee asked the PEC to analyze the dosing distribution for nasal corticosteroids within DoD and propose BCF changes if appropriate. The committee emphasized that it did not wish to make further additions to the BCF without complete information, but agreed that the presence of an additional nasal corticosteroid agent on the BCF could potentially spur competitive pricing.

5. *Consideration of Niaspan (niacin extended release; Kos Pharma) for the BCF*— Niacin is well known to have a positive effect on the lipid profile of patients with dyslipidemias and is particularly effective in raising high-density lipoprotein cholesterol (HDL-C). Patient intolerance to the common side effects of flushing and pruritis limits the usefulness of niacin in clinical practice. Sustained release forms of niacin may be tolerated better than immediate release forms, but sustained release forms have been associated with a higher incidence of liver toxicity. Niaspan is promoted as a once-daily product that is not associated with a higher incidence of liver toxicity. Niaspan costs significantly more than other sustained release forms of niacin.

   The committee is concerned that patient tolerance of niacin may be related more closely to the educational efforts regarding drug dosing than the specific dosage form that is used. Due to the limited data available, the committee also has concerns about the potential for liver toxicity with Niaspan. The committee asked the PEC to further investigate the associations between niacin dosage forms and patient tolerance and liver toxicity. The PEC will also evaluate usage patterns of all niacin products within DoD and obtain input from MTFs regarding the potential addition of Niaspan to the BCF. The PEC will provide a recommendation regarding the BCF status of Niaspan at the next meeting.

6. *Request for removal of dipivefrin ophthalmic solution (Propine, generics) from the BCF and review of ophthalmic glaucoma agents*—The committee removed dipivefrin from the BCF. Dipivefrin has been reported to have a relatively high rate of side effects relative to other available agents, which are at least equally effective. Dipivefrin represents approximately 2% of usage of glaucoma agents in DoD by number of bottles purchased, compared to timolol (Timoptic, generics) 33%, latanoprost (Xalatan) 21%, dorzolamide (Trusopt) 12%, and multiple other agents each representing 7% or less of total usage. CDR Matt Nutaitis, an ophthalmologist and allergy specialist, will undertake a review of ophthalmic glaucoma agents and make recommendations for BCF changes at the next meeting. An interim report is due to the co-chairs by 11 April.

7. *BCF status of cisapride (Propulsid; Janssen)*—The committee removed cisapride from the BCF based on recent FDA recommendations and labeling changes aimed at avoiding use of the medication in patients at known risk of rare but serious cardiac events associated with use of the drug. Labeling changes include the recommendation that an electrocardiogram, serum electrolytes, and serum creatinine be performed prior to initiation of therapy, as well as a list of contraindicated drugs and underlying conditions. With the continuing reports of heart rhythm disorders and deaths associated with use of cisapride, the committee agreed that the benefits of the drug are not likely to outweigh the known risks except for selected patients.

8. *Status of human chorionic gonadotropin injection in the NMOP*—The committee added human chorionic gonadotropin injection to the NMOP Covered Injectables list. This agent has historically been provided by the NMOP and was inadvertently omitted when the Covered Injectables list was formulated.

7. ADJOURNMENT: The meeting adjourned at 1600 hours. The next meeting will be held on Thursday, 11 May 2000, at Fort Sam Houston, Texas. All agenda items should be submitted to the co-chairs no later than 11 April 2000.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

LIST OF APPENDICES

APPENDIX A: Minutes of the Interim Meeting of the DoD P&T Committee, 26 Jan 00, concerning identification of drugs for the Advances in Medical Practice (AMP) Program;

APPENDIX B: Consolidated List of Drugs Recommended for the AMP Program by the DoD P&T Committee. **Note**: This list of drugs is **not** final. The list has been submitted to AMP officials, TMA officials, and resource management officers for final approval. MTFs will be notified of the final list of drugs and finalized procedures for reimbursement for expenditures on drugs covered by the AMP program as soon as they are approved.

APPENDIX C: NMOP Preferred Drug Program Report

APPENDIX D: Formulary Changes

APPENDIX E: Reports Due to the Committee

APPENDIX A: Minutes of the Interim Meeting of the DoD P&T Committee, 26 Jan 00, Concerning Identification of Drugs for the Advances in Medical Practice (AMP) Program

NOTE: After this interim meeting and at the request of AMP program officials, the P&T committee co-chairs subsequently recommended more drugs for coverage by the AMP program. See Appendix B for the consolidated list of all drugs recommended by the DoD P&T Committee for coverage under the AMP program.

Department of Defense
Pharmacoeconomic Center

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MCCS-GPE

26 January 2000

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of an Interim Meeting of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee—Advances in Medical Practice (AMP) Program

1. In accordance with Health Affairs policy 98-025, an interim meeting of the DoD P&T Committee convened via teleconference at 1300 on 26 January 2000. The purpose of this meeting was to identify new drug usage that should be supported by Advances in Medical Practice (AMP) funds.

2. MEMBERS Participating in the Teleconference:

COL Daniel D. Remund, MS	Co-chairman
CDR Terrance Egland, MC	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Danielle Doyle	Army
LCDR Kevin Cook, MSC	Navy
LTC John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard

COL Daniel D. Remund voted as proxy for CDR Matt Nutaitis.
COL (select) Bill Sykora was absent.

3. OTHERS Participating in the Teleconference:

COL W. Michael Heath	Pharmacy Consultant, USA
COL Ardis Meier	Associate Chief, BSC for Pharmacy, USAF
CAPT Greg Hall	Director, Pharmacy Department, Portsmouth Naval Hospital

4. NEW BUSINESS

A. The AMP funds allocated for MTF pharmacies are intended to provide "seed money" to help MTFs purchase new drugs that are clinically beneficial, but which MTF pharmacies tend not to provide to patients because of insufficient funding. The plan is to use AMP money to support the usage of certain new drugs for the first year or two until funds can be programmed into the MTF budget "base" to support ongoing use of the drugs. The DoD Pharmacy Board of Directors is working with resource managers to design a mechanism to reimburse MTFs for their usage of drugs covered by the AMP program.

B. Based on recommendations provided by the PEC, the Committee recommends that AMP funds should be used to completely reimburse MTFs for FY 00 usage of the following drugs:

1. Etanercept (Enbrel)
2. Infliximab (Remicade)
3. Leflunomide (Arava)
4. Oral ribavirin / interferon alfa-2b combination (Rebetron)
5. Palivizumab (Synagis)
6. Coagulation Factor VIIa (Recombinant) (NovoSeven)

[Note: The Committee did **NOT** add these drugs to the Basic Core Formulary (BCF).]

C. Based on recommendations provided by the PEC, the Committee recommends that AMP funds should be used to reimburse MTFs for their FY 00 usage of COX-2 inhibitors as outlined below:

1. Use AMP funds to reimburse MTFs for 50% of their expenditures for COX-2 inhibitors. The reimbursement would occur regardless of the status of COX-2 inhibitors on the MTF formulary. [Note: The 50% reimbursement rate provides a financial incentive for MTFs to target the use of COX-2 inhibitors to patients who are increased risk for gastrointestinal problems secondary to NSAID use.]

2. Do not add a COX-2 inhibitor to the BCF.

3. Do not stipulate on the BCF that MTFs must have a COX-2 inhibitor on their formularies. Each MTF decides for itself whether to have a COX-2 inhibitor(s) on the MTF formulary.

4. Require MTFs to use prescribing guidelines, prior authorization, or other means to target the use of COX-2 inhibitors to patients who are at increased risk for GI problems secondary to NSAID use.

5. Pursue pricing agreements that are based on the status of COX-2 inhibitors on the MTF formulary.

6. Any new COX-2 inhibitor will be considered for addition to the list of drugs covered by AMP funds.

D. The PEC will provide cost projections for the drugs covered by the AMP program to the DoD Pharmacy Board of Directors and the AMP program managers.

5. ADJOURNMENT: The meeting adjourned at 1445 hours.

<signed>

DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>

TERRANCE EGLAND
CDR, MC, USN
Co-chair

APPENDIX B: Consolidated List of Drugs Recommended for the AMP Program by the DoD P&T Committee.

NOTE: This list of drugs is **not** final. The list has been submitted to AMP officials, TMA officials, and resource management officers for final approval. MTFs will be notified of the final list of drugs and finalized procedures for reimbursement for expenditures on drugs covered by the AMP program as soon as they are approved.

Background: The pharmacy portion of AMP funding for FY00 is intended to provide "seed money" to purchase drugs that are clinically beneficial but which MTF pharmacies tend not to provide because of insufficient funds. The drugs covered under the AMP program are newly approved, have had new indications approved since initial approval, or have an extremely high unit cost. Under current planning, AMP money will support the usage of certain new drugs for a period of two to three years until funds can be programmed into the MTF budget "base" to support the ongoing use of the drugs.

Department of Defense Pharmacy and Therapeutics (DoD P&T) Committee Recommendations: On 26 January 2000, the Department of Defense Pharmacy and Therapeutics (DoD P&T) committee recommended that the first seven drugs listed in Table 1 be funded through the AMP program. On 9 Feb 00, additional drugs were selected by an interim decision of committee co-chairs. Currently, none of the selected drugs are listed on the Basic Core Formulary (BCF). The committee recommended that none of the drugs be added to the BCF. The committee recommended using AMP funds to reimburse MTFs for 100% of their expenditures for all selected drugs with the exception of COX-2 inhibitors.

For COX-2 inhibitors, the committee recommended that AMP funds be used to reimburse MTFs for 50% of their costs (e.g., if a MTF spent $20,000 on COX-2 inhibitors for a given month, the AMP program would reimburse the MTF $10,000). The 50% reimbursement provision for COX-2 inhibitors should provide the financial incentive for MTFs to make these drugs more available to patients with a valid clinical need. Reimbursement at 100% would discourage MTF efforts to ensure appropriate use of these drugs. Lastly, the committee recommended that MTFs be required to use prescribing guidelines, prior authorization, or other means to target the use of COX-2 inhibitors to patients who are at increased risk for GI problems secondary to NSAID use.

Table 1 (continued): Consolidated List of Drugs Recommended for the AMP Program by the DoD P&T Committee.

Drug	Indication
These drugs selected for funding through the AMP program by the DoD Pharmacy & Therapeutics Committee via teleconference, 26 Jan 00.	
Etanercept (Enbrel; Immunex / Wyeth-Ayerst)	Moderately to severely active rheumatoid arthritis (RA) and polyarticular-course juvenile rheumatoid arthritis in patients with an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). May be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
Infliximab (Remicade; Centocor)	Moderately to severely active Crohn's disease for the reduction of signs and symptoms in patients who have an inadequate response to conventional therapies; and treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s). Recently approved in combination with methotrexate for reduction in signs and symptoms of RA in patients who have had an inadequate response to methotrexate.
Leflunomide (Arava; Hoechst Marion Roussel)	Active RA to reduce signs and symptoms and to retard structural damage as evidenced by x-ray erosions and joint space narrowing in adults
Coagulation Factor VIIa (Recombinant) (NovoSeven; Novo Nordisk)	Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.
Oral ribavirin / interferon alfa-2b combination (Rebetron; Schering)	Treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy, approved in December 98 for patients not previously treated with interferon.
Palivizumab (Synagis; MedImmune)	Prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease
Cyclooxygenase-2 (COX-2) inhibitors— Celecoxib (Celebrex; Searle/Pfizer); Rofecoxib (Vioxx; Merck)	Celecoxib is indicated for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA), and was very recently approved for reduction in the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). Rofecoxib is indicated for OA, acute pain, and primary dysmenorrhea. NOTE: For COX-2 inhibitors, the committee recommended that AMP funds be used to reimburse MTFs for 50% of their costs.
These drugs selected for funding through the AMP program by an interim decision of DoD Pharmacy & Therapeutics Committee co-chairs, 9 Feb 00.	
Glycoprotein IIb/IIIa inhibitors— • Eptifibatide (Integrilin; COR) • Tirofiban (Aggrastat; Merck) • Abciximab (ReoPro; Lilly)	Abciximab indicated for use as an adjunct to PTCA, tirofiban indicated for acute coronary syndrome, and eptifibatide indicated for both acute coronary syndrome or treatment of patients undergoing percutaneous coronary intervention (PCI)

Table 1 (continued): Consolidated List of Drugs Recommended for the AMP Program by the DoD P&T Committee

Drug	Indication
Immunosuppressants— • Cyclosporine (various manufacturers) • Mycophenolate mofetil (Cellcept; Roche) • Sirolimus (Rapamune; Wyeth-Ayerst) • Tacrolimus (Prograf; Fujisawa)	Cyclosporine: Prophylaxis of organ rejection in kidney, liver, and heart transplantation. RA (Neoral only), psoriasis (Neoral only). Multiple unapproved indications. Mycophenolate mofetil: Prophylaxis of organ rejection in kidney or heart transplantation. Sirolimus: Prophylaxis of organ rejection in kidney transplantation. Tacrolimus: Prophylaxis of organ rejection in liver transplantation.
Dornase alfa (Pulmozyme)	Daily administration in conjunction with standard therapies in the management of cystic fibrosis patients to reduce the frequency of respiratory infections requiring parenteral antibiotics and to improve pulmonary function
Interferon gamma 1b (Actimmune)	Reduction of the frequency and severity of serious infections associated with chronic granulomatous disease
$Alpha_1$-proteinase inhibitor (Prolastin)	Chronic replacement in patients with congenital alpha1-antitrypsin deficiency and clinically demonstrable panacinar emphysema.
Temozolomide (Temodar)	Oral chemotherapy agent for adult patients with refractory anaplastic astrocytoma; pending NDAs for other conditions.
Trastuzumab (Herceptin)	Treatment of metastatic breast cancer in patients with tumors that overexpress the HER2 protein
Rituzimab (Rituxan)	Treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's Lymphoma.
Drugs for MS • Interferon beta 1a (Avonex) • Interferon beta 1b (Betaseron) • Glatiramer acetate (Copaxone)	Treatment of relapsing/remitting multiple sclerosis.
Colony Stimulating Factors • Filgrastim (Neupogen) • Sargramostim (Leukine)	To reduce the incidence and duration of neutropenia-related sequelae (e.g., infection, fever) associated with myelosuppressive chemotherapy, bone marrow transplant, severe chronic neutropenia, etc., and for the mobilization of hematopoietic progenitor cells into the peripheral blood for leukapheresis collection.

Table 1 (continued): Consolidated List of Drugs Recommended for the AMP Program by the DoD P&T Committee

Drug	Indication
Irinotecan (Camptosar)	Metastatic carcinoma of the colon or rectum.
Gemcitabine (Gemzar)	First-line treatment for locally advanced or metastatic pancreatic cancer and in combination with cisplatin for first-line treatment of inoperable, locally advanced or metastatic non-small cell lung cancer
Epoetin alfa [Recombinant human erythropoietin] (Epogen, Procrit)	Reduction of allogeneic blood transfusion in surgery patients and treatment of anemia from various causes, including chronic renal failure, zidovudine therapy in HIV-infected patients, and chemotherapy.
Becaplermin (Regranex)	Treatment of diabetic neuropathic ulcers in conjunction with debridement and good ulcer care.

APPENDIX C: NMOP Preferred Drug Program Report

The NMOP Preferred Drug Program

The purpose of the NMOP Preferred Drug Program is to encourage the use of drugs that are preferred on the basis of relative effectiveness, safety, and cost. The NMOP calls the prescriber on each new prescription for a non-preferred agent and requests a switch to a preferred drug. If the prescriber declines or if the prescriber cannot be contacted, the prescription is filled as written.

Methods of Calculating Cost Avoidance

The NMOP Preferred Drug Program achieves cost avoidance by shifting prescription market share to the preferred drugs. In general, cost avoidance is estimated by subtracting the actual expenditures for preferred and non-preferred drugs from the expenditures that would have been expected if the Preferred Drug Program did not exist (cost avoidance = expected expenditures – actual expenditures). The specific method used to calculate cost avoidance for a given set of preferred and non-preferred drugs depends on the distribution of prescriptions that would have been expected for preferred and non-preferred drugs if the Preferred Drug Program did not exist.

1. *Distribution of prescriptions expected to remain constant if Preferred Drug Program did not exist*—Examples include diltiazem extended release, nifedipine extended release, and the nonsteroidal anti-inflammatory drugs (NSAIDs).

   Calculation of "expected" expenditures is straightforward because we simply apply the baseline market share percentages that existed before the Preferred Drug Program was implemented. First, calculate the expected number of prescriptions for each preferred and non-preferred drug by multiplying the actual total number of prescriptions filled during the month by the percentage of the prescription market that each drug represented before the Preferred Drug Program was implemented. Second, calculate the expected expenditures by multiplying the expected number of prescriptions for each preferred and non-preferred drug by the current cost per prescription for that drug and then sum the products. Calculate the cost avoidance by subtracting the actual expenditures from the expected expenditures. [NOTE: This method accounts for the impact of both new and refill prescriptions on cost avoidance.]

2. *Distribution of prescriptions expected to change even if Preferred Drug Program did not exist*—Urinary agents (preferred drug: oxybutynin generic; non-preferred drugs Detrol, Ditropan XL) are an example. Because Detrol and Ditropan XL are relatively new agents, market share percentages are likely to change even if the Preferred Drug Program did not exist.

   Calculation of expected expenditures is not straightforward because we cannot simply apply the baseline market share percentages that existed before the Preferred Drug Program was implemented. We do not have a method for predicting what the market share percentages would have been in the absence of the Preferred Drug Program. For this set of drugs, cost avoidance was calculated by multiplying the number of prescriptions switched for each target drug by the difference in average cost per prescription between the target drug and oxybutynin. This method only accounts for the cost avoidance for the single new prescription that was switched at the time

of the phone call. It does not account for the cost avoidance that would be associated with any prescription refills. This method underestimates the cost avoidance.

3. *Drugs/drug classes for which the quantity dispensed (and cost) per prescription is highly variable*—An example is the anti-herpes drugs (preferred drug: acyclovir generic; non-preferred drugs Valtrex, Famvir). Analysis of the cost avoidance associated with this set of drugs proved difficult. Dosing regimens and quantities dispensed per prescripton vary widely for anti-herpes drugs according to the disease being treated (herpes zoster, herpes simplex) and the reason for use (treatment, prophylaxis). The cost avoidance calculation methods described above yielded results that do not readily correlate either with reported switches or the market share of acyclovir. For this reason, a cost avoidance estimate is not provided for the anti-herpes drugs in this report. Results of continued analysis will be presented at the May 00 meeting.

Non-Preferred/Preferred Drug Pairs

1. Extended Release Diltiazem

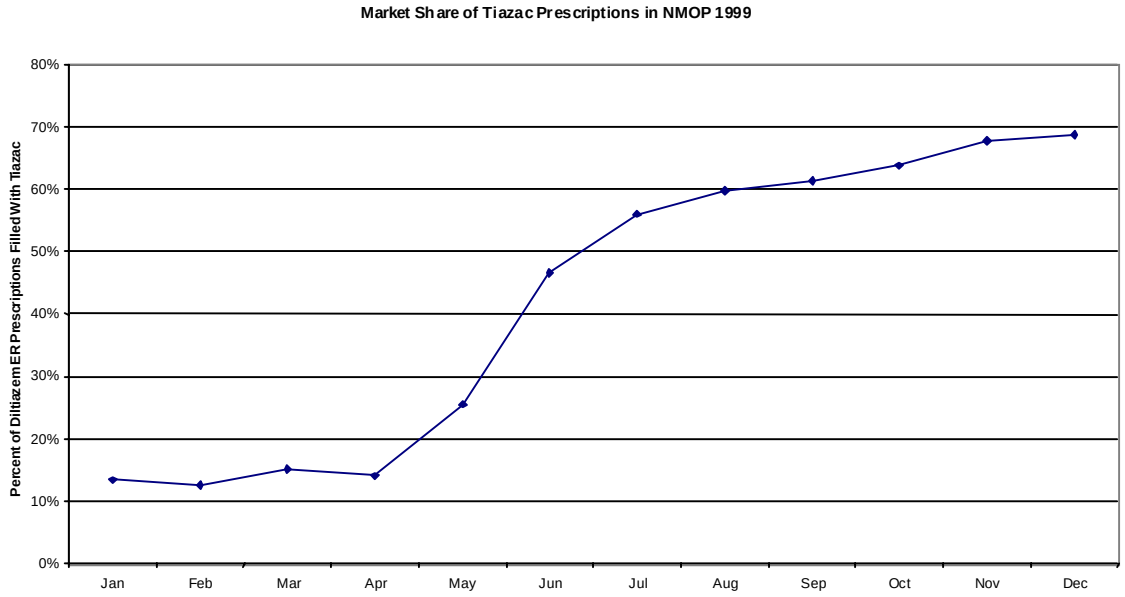
Tiazac was designated as the preferred diltiazem ER product in NMOP in May 99. Non-preferred diltiazem products include Cardizem CD, Diltia XT, Dilacor XR, and generic diltiazem ER.

Table 1: Prescriptions for Non-Preferred Diltiazem ER products in NMOP, Jun – Dec 99

Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	**Jun-Dec**
New Rxs Received	720	661	573	395	328	291	346	**3314**
Prescriber Contacts	653	616	540	352	301	263	311	**3036**
Switches	514	495	434	255	215	189	217	**2319**
Switch Rate*	71%	75%	76%	65%	66%	65%	63%	**70%**

* Percentage of new prescriptions received for non-preferred drugs that were switched to Tiazac

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance

Month	**Jun 99**	**Jul 99**	**Aug 99**	**Sep 99**	**Oct 99**	**Nov 99**	**Dec 99**	**Jun-Dec 99**
Cost avoidance	$21,796	$27,287	$31,098	$29,017	$28,112	$34,592	$30,123	**$202,025**

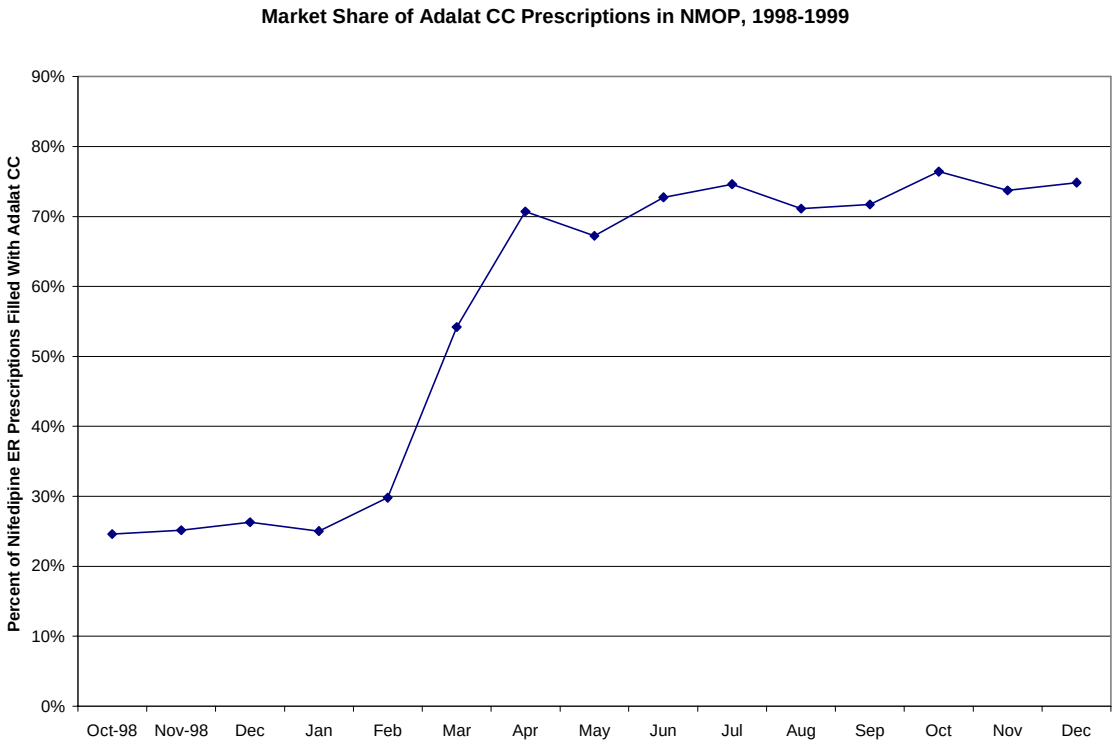
2. Extended Release Nifedipine

In Nov 98 the DOD P & T Committee selected Adalat CC as the preferred nifedipine ER product. Procardia XL is non-preferred.

Table 2: Prescriptions for Non-Preferred Nifedipine ER in NMOP, Jun – Dec 1999								
Month	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jun - Dec**
New Rxs Received	379	142	125	139	124	127	153	**1189**
Prescriber Contacts	345	132	102	120	114	101	129	**1043**
Switches	254	91	66	63	61	58	90	**683**
Switch Rate*	67%	64%	53%	45%	49%	46%	59%	**57%**

* Percentage of new prescriptions received for non-preferred drugs that were switched to Adalat CC

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance

Month	**Jun 99**	**Jul 99**	**Aug 99**	**Sep 99**	**Oct 99**	**Nov 99**	**Dec 99**	**Jun – Dec 99**
Cost Avoidance	$27,494	$26,624	$24,962	$24,510	$27,938	$26,122	$24,173	**$181,823**

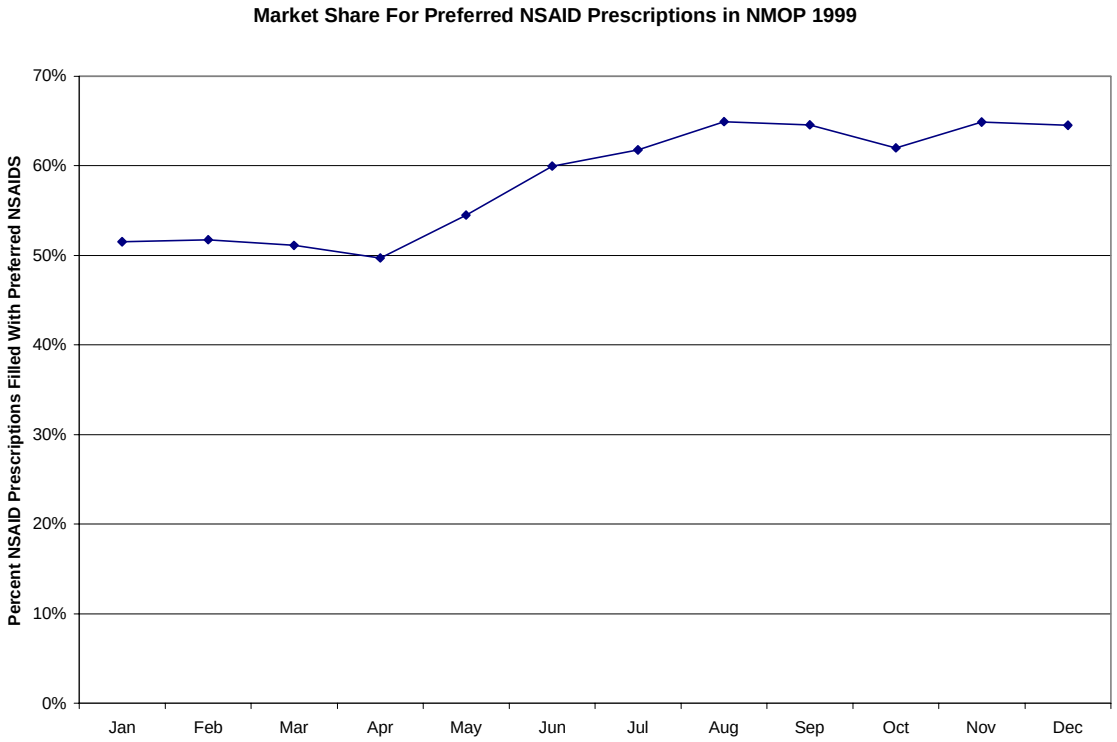
3. NSAIDS

Generic NSAIDs are preferred. Daypro, Relafen, Voltaren XR, Lodine XL, and Naprelan are non-preferred. Program started mid-May 99

Table 3: Prescriptions For Non-Preferred NSAIDs in NMOP, Jun – Dec 1999								
Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	**Jun - Dec**
New Rxs Received	617	596	549	456	432	361	434	**3445**
Prescriber Contacts	525	504	492	385	367	304	384	**2961**
Switches	244	220	248	153	150	140	136	**1291**
Switch Rate*	40%	37%	45%	34%	35%	39%	31%	**37%**

* Percentage of new prescriptions received for non-preferred drugs that were switched to generic NSAIDs

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance

Month	**Jun 99**	**Jul 99**	**Aug 99**	**Sep 99**	**Oct 99**	**Nov 99**	**Dec 99**	**Jun – Dec 99**
Cost Avoidance	$21,771	$19,929	$27,670	$29,294	$25,052	$36,465	$29,364	**$189,584**

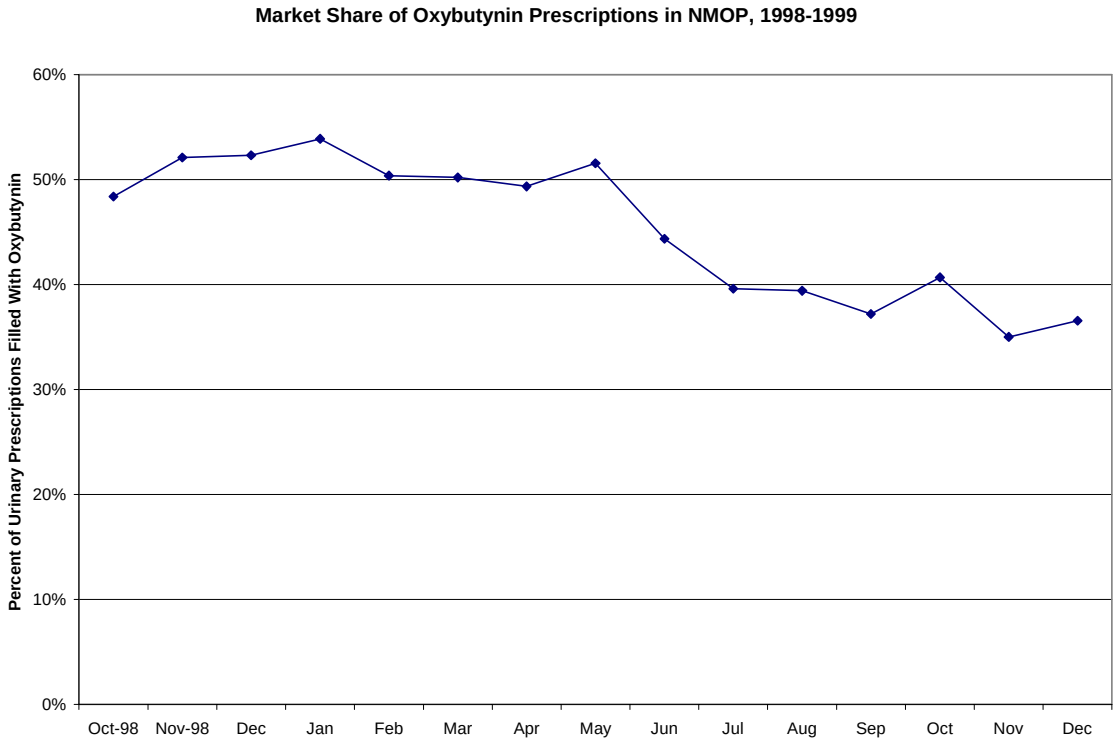
4. Urinary Agents

In November 1998, the DOD P & T Committee selected oxybutynin generic as the preferred urinary agent. Detrol and Ditropan XL are non-preferred.

Table 4: Prescriptions for Non-Preferred Urinary Drugs in NMOP, Jun – Dec 99								
Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	**Jun – Dec**
New Rxs Received	224	183	270	271	308	325	363	**1944**
Prescriber Contacts	195	158	233	236	270	256	331	**1679**
Switches	80	40	76	69	95	88	105	**553**
Switch Rate*	36%	22%	28%	25%	31%	27%	29%	**28%**

* Percentage of new prescriptions received for non-preferred drugs that were switched to oxybutynin generic

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



Monthly Cost Avoidance

Month	**Jun 99**	**Jul 99**	**Aug 99**	**Sep 99**	**Oct 99**	**Nov 99**	**Dec 99**	**Jun – Dec 99**
Cost Avoidance	$7,735	$4,355	$6,823	$6,575	$8,769	$8,414	$10,271	**$52,942**

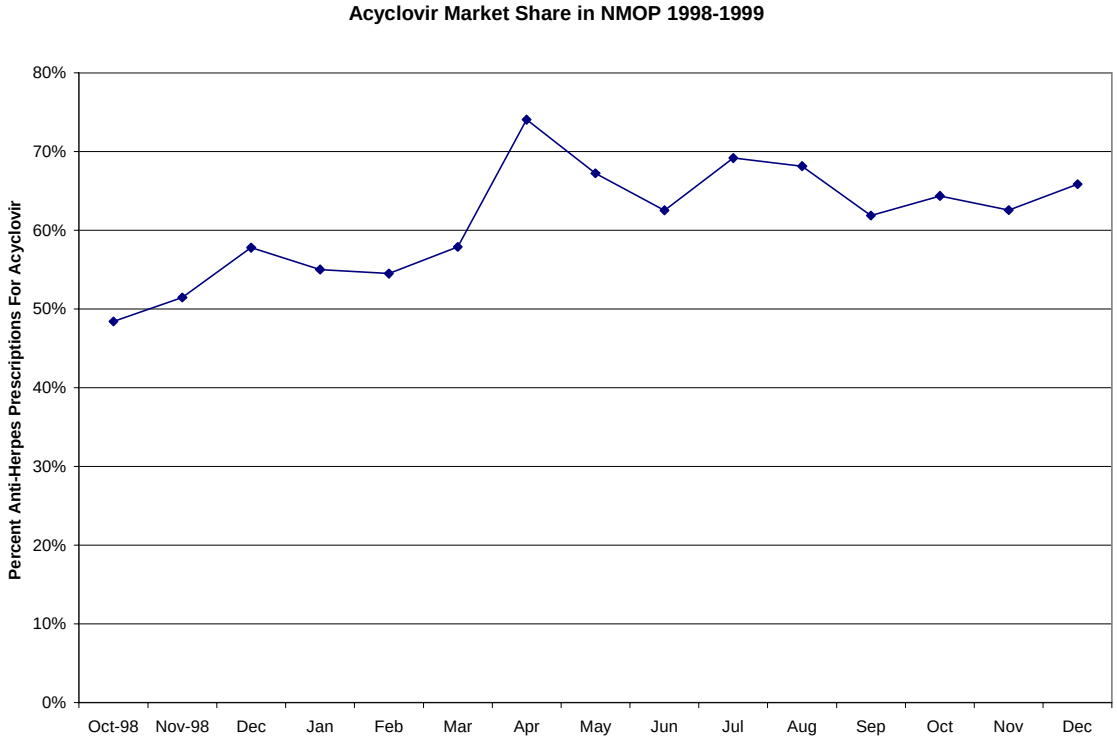
5. Anti-Herpes Drugs

Generic acyclovir is the preferred anti herpes drug. Famvir and Valtrex are non-preferred.

Table 5: Prescriptions for Non-Preferred Anti-Herpes Drugs in NMOP, Jun – Dec 1999								
Month	Jun	Jul	Aug	Sep	Oct	Nov	Dec	**Jun – Dec**
New Rxs Received	77	52	51	44	60	62	70	**416**
Prescriber Contacts	68	44	39	30	41	46	57	**325**
Switches	28	14	21	21	15	17	17	**133**
Switch Rate*	36%	27%	41%	48%	25%	27%	24%	**32%**

* Percentage of new prescriptions received for non-preferred drugs that were switched to acyclovir

Market Share Data (From NMOP adjudicated and non-adjudicated prescription claims files, Defense Supply Center Philadelphia)



APPENDIX D: FORMULARY CHANGES

I. BCF changes

A. BCF changes as a result of the 26 Jan 00 Interim Meeting:

1. Addition of the following:

a. metformin
b. tamoxifen
c. alendronate
d. citalopram
e. fluoxetine
f. paroxetine
g. sertraline
h. sumatriptan autoinjector

2. Specification that military treatment facilities (MTFs) must have at least one agent from each of the following classes on their formularies:

a. Oral serotonin 5-HT_1 receptor agonists (naratriptan, rizatriptan, sumatriptan, zolmitriptan)
b. Low molecular weight heparins/heparinoids (ardeparin, dalteparin, danaparoid, enoxaparin)
c. Leukotriene antagonists (montelukast, zafirlukast, zileuton)
d. Second-generation antihistamines (cetirizine, fexofenadine, loratadine)

B. Dipivefrin ophthalmic solution (Propine) removed from the BCF

C. Cisapride (Propulsid) removed from the BCF

II. NMOP Formulary Changes

A. Added to the NMOP Formulary:

1. Ethinyl estradiol / norethindrone acetate tablets (FemHRT; Parke Davis)
2. Exemestane tablets (Aromasin; Pharmacia & Upjohn)
3. Estradiol / norgestimate tablets (Ortho-Prefest; Ortho McNeil)
4. Aspirin / dipyridamole extended release capsules (Aggrenox; Boehringer-Ingelheim)
5. Moxifloxacin hydrochloride tablets (Avelox; Bayer)
6. Gatifloxacin tablets (Tequin; Bristol Myers Squibb)
7. Oxcarbazepine tablets (Trileptal; Novartis)

B. Excluded from the NMOP Formulary

1. Oseltamivir phosphate capsules (Tamiflu; Roche)
2. Bexarotene capsules (Targretin; Ligand Pharma)

APPENDIX D (continued): FORMULARY CHANGES

C. Pantoprazole (Protonix; Wyeth-Ayerst) listed as a “non-contracted drug” on the NMOP Formulary due to contractual requirements of the PPI contract

D. Human chorionic gonadotropin injection (various manufacturers) added to the NMOP Covered Injectables list (has historically been provided by the NMOP).

III. Quantity Limit Change (NMOP and retail network): Quantity limit for azithromycin (Zithromax) 250-mg tablets changed from 6 tablets per 30 days to 10 tablets per 30 days for both the NMOP and the retail network.

APPENDIX E: REPORTS DUE TO THE COMMITTEE

I. *Non-preferred/preferred drug pairs standing report* (see Paragraph 5B) — CDR Mark Brouker (PEC). Interim report due to co-chairs by April 11, full report to committee at the next meeting.

II. *Quantity limits for topicals* (see Paragraph 5C2)— The subcommittee will supply additional information concerning usage patterns for the five high-cost topicals identified at the last meeting [imiquimod (Aldara); calcipotriene (Dovonex); altitretinoin (Panretin); becaplermin (Regranex); and tazarotene (Tazorac)]. Subcommittee members: Bill Hudson (chair); MAJ George Jones; MAJ Mickey Bellemin; Ray Nan Berry (Foundation Health); Kirby Davis (Anthem Alliance); William Hudson (Humana); Gene Lakey (TriWest); and Ron McDonald (Sierra Military Health Services). Interim report due to co-chairs by April 11, full report to committee at the next meeting.

III. *Cost-efficiency of prior authorizations in the NMOP standing report* (see Paragraph 5D)—MAJ Bellemin. Interim report due to co-chairs by April 11, full report to committee at the next meeting.

IV. *Prior authorization for oral antifungals* (see Paragraph 5E)— A subcommittee consisting of CDR Egland (chair); Paul Vasquez (DSCP), MAJ Bellemin (DSCP), and MAJ Ed Zastawny (PEC) will develop a proposed PA program to be presented to the committee at the next meeting. An interim report is due to co-chairs by 11 Apr 99.

V. *Prior authorization for fertility drugs* (see Paragraph 6A2)—CAPT Charlie Hostettler (TMA) will submit authorization criteria for fertility agents to the co-chairs. The co-chairs will finalize the criteria for approval at the May P&T Committee meeting. CDR Egland is the point of contact for this action.

VI. *Growth hormone subcommittee* (see Paragraph 6A4)—(Bill Hudson (chair); MAJ George Jones; MAJ Mickey Bellemin; Ray Nan Berry (Foundation Health); Kirby Davis (Anthem Alliance); William Hudson (Humana); Gene Lakey (TriWest); Ron McDonald (Sierra Military Health Services)) — A business case analysis that covers off-label uses and uses for adults, as well as completed prior authorization criteria (including required forms) with supporting documentation, is due to CDR Egland by 11 Apr 00.

VII. *Portability of Prior Authorizations* (see Paragraph 6A5)—MAJ Bellemin (DSCP) will investigate the feasibility of a program to provide for portability of prior authorizations completed by the NMOP or the MCSCs and report back to the committee at the next meeting.

VIII. *Nasal Corticosteroids* (see Paragraph 6D4)—The PEC will analyze the dosing distribution for nasal corticosteroids within DoD and make recommendations if indicated, to be presented to the committee at the next meeting. An interim report is due to co-chairs by 11 Apr 99.

IX. *Niaspan (niacin extended release; Kos Pharma)* (See Paragraph 6D5)—The PEC will provide information to the committee at the next meeting regarding the associations between niacin dosage forms and patient tolerance and liver toxicity. The PEC will also describe usage patterns of niacin products within DoD and convey input from MTFs regarding the potential addition of Niaspan to the BCF.

X. *Review of Ophthalmic Glaucoma Agents* (See Paragraph 6D6) —CDR Matt Nutaitis will review the ophthalmic glaucoma agents and make recommendations for BCF changes to be submitted to the committee at the next meeting. An interim report is due to the co-chairs by 11 April.

Department of Defense
Pharmacoeconomic Center

1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE 26 January 2000

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of an Interim Meeting of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee—Program Budget Decision (PBD) No. 041

1. In accordance with Health Affairs policy 98-025, an interim meeting of the DoD P&T Committee convened via teleconference at 1200 on 26 January 2000. The purpose of this meeting was to identify additions to the Basic Core Formulary (BCF) in response to additional funding for military pharmacies provided by the Program Budget Decision (PBD) No. 041.

2. MEMBERS Participating in the Teleconference:

COL Daniel D. Remund, MS	Co-chairman
CDR Terrance Egland, MC	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Danielle Doyle	Army
LCDR Kevin Cook, MSC	Navy
COL (select) John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard

COL Daniel D. Remund voted as proxy for CDR Matt Nutaitis.
COL (select) Bill Sykora was absent.

3. OTHERS Participating in the Teleconference:

COL W. Mike Heath	Pharmacy Consultant, USA
COL Ardis Meier	Associate Chief, BSC for Pharmacy, USAF
CAPT Greg Hall	Director, Pharmacy Department, Portsmouth Naval Hospital

4. NEW BUSINESS

A. The TRICARE Management Activity (TMA) and the DoD Pharmacy Board of Directors determined that funds allocated to MTF pharmacies through PBD No. 041 should be used to increase and standardize the availability of drugs at MTF pharmacies. The DoD Pharmacoeconomic Center (PEC) developed a set of recommended changes and additions to the BCF for the DoD P&T Committee to consider.

B. The Committee added the following drugs to the BCF:

1. Metformin
2. Tamoxifen
3. Alendronate
4. Citalopram
5. Fluoxetine
6. Paroxetine
7. Sertraline
8. Sumatriptan autoinjector

C. The Committee decided to modify the BCF as follows:

1. The BCF will specify that MTFs must have at least one low molecular weight heparin/heparinoid (aldeparin, dalteparin, danaparoid, enoxaparin) on the MTF formulary. The MTF decides which low molecular weight heparin/heparinoid(s) to have on the MTF formulary.

2. The BCF will specify that MTFs must have at least one leukotriene antagonist (monelukast, zafirlukast, zileuton) on the MTF formulary. The MTF decides which leukotriene antagonist(s) to have on the MTF formulary.

3. The BCF will specify that MTFs must have at least one second-generation antihistamine (cetirizine, fexofenadine, loratadine) on the MTF formulary. The MTF decides which second generation antihistamine(s) to have on the MTF formulary.

4. The BCF will specify that MTFs must have at least one oral triptan (naratriptan, rizatriptan, sumatriptan, zolmitriptan) on the MTF formulary. The MTF decides which oral triptan to have on the MTF formulary.

D. The Committee decided not to add gabapentin to the BCF.

E. The Committee stressed that the changes and additions to the BCF are dependent on the PBD funds actually being used to support MTF pharmacy pharmaceutical purchases.

5. ADJOURNMENT: The meeting adjourned at 1400 hours. The committee immediately reconvened to determine which drugs should be covered by Advances in Medical Practice (AMP) funding.

<signed>
DANIEL D. REMUND
COL, MS,USA
Co-chairman

<signed>
TERRANCE EGLAND
CDR, MC,USN
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Pharmacoeconomic Center

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MCCS-GPE 18 November 1999

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 18 November 1999, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, TX.

2. MEMBERS PRESENT:

COL Daniel D. Remund, MS	Co-chairman
CDR Terrance Egland, MC	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Danielle Doyle	Army
CDR Matt Nutaitis, MC	Navy
LCDR Kevin Cook, MSC	Navy
COL (select) Bill Sykora, MC	Air Force
LTC John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs (alternate)
COL George Crawford, MS	Joint Readiness Clinical Advisory Board
LTC Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia (DSCP)
Trevor Rabie	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services

3. OTHERS PRESENT:

CAPT Charlie Hostettler, MSC	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
David Chicoine	Uniformed Services Family Health Plans (USFHP)
COL Jeffery Meffert, MC	BAMC, Dermatology
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
LCDR Mark Richerson, MSC	DoD Pharmacoeconomic Center
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
MAJ Ed Zastawny, BSC	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Mark Petruzzi	Merck-Medco
LTC Gary Blamire, BSC	TRICARE Southwest Lead Agent Office

4. ADMINISTRATIVE ISSUES:

A. Introduction of new members and attendees: Trevor Rabie, MD, is a new committee member representing the Uniformed Services Family Health Plans (USFHP). Howard Altschwager is a new attendee as legal counsel for the DoD P&T Committee.

B. The minutes from the 13 Aug 99 meeting were accepted as written.

C. The co-chairs reported an interim decision to temporarily discontinue the 10-tablet quantity limit for zolpidem (Ambien) because almost all NMOP prescriptions were written for more than 10 tablets and many patients complained about the quantity limit. The labeling for zolpidem recommends that therapy should generally be limited to 7 to 10 days of use, but medical literature supports longer-term use of zolpidem for patients with chronic insomnia. The committee decided that zolpidem should be subject to the standard quantity limit of a 30-day supply for controlled substances.

5. OLD BUSINESS

A. Non-preferred/preferred drug pairs in the NMOP

1. CDR Brouker (PEC) reported that the cumulative switch rates from non-preferred to preferred drugs observed from 29 May 99 to 6 November 99 were similar to the switch rates observed from 29 May 99 to 31 July 99. The overall switch rate was 57%. The committee removed Zileuton (Zyflo) from the list of non-preferred drugs because the NMOP received only six prescriptions for the drug in 24 weeks, and only one of those prescriptions was switched to a preferred drug.

2. MAJ Bellemin reported that Merck-Medco has not yet implemented the new non-preferred/preferred drug pairs approved at the August 1999 P&T meeting. Merck-Medco will implement them on 1 Dec 99.

3. CDR Brouker will design a standard report for monitoring processes and outcomes related to non-preferred/preferred drug pairs in the NMOP. The report will include switch rate data, the resulting distribution of prescriptions within the pertinent drug classes, and the estimated cost avoidance. CDR Brouker will submit a draft of the report to the committee co-chairs not later than 17 December 1999. CDR Brouker will submit the finalized version of the report to the committee at the next meeting.

B. Prior authorizations in the NMOP

1. MAJ Bellemin reported that Merck-Medco has implemented prior authorization processes for celecoxib (Celebrex), rofecoxib (Vioxx), etanercept (Enbrel), and sildenafil (Viagra). He will present data concerning the cost-efficiency of prior authorizations at the next meeting.

2. Military treatment facility (MTF) providers are concerned about the amount of time they spend dealing with phone calls and fax forms from Merck-Medco for drugs requiring prior authorization. MTF providers requested that prior authorization fax forms be posted on the PEC website so that they could save time by filling out the form and having the patient submit it along with the prescription to the NMOP. Mark Petruzzi stated that Merck-Medco would concur with the proposal as long as the actual form approved by Merck Medco was posted on the PEC website. He further stated that prescriptions would be filled without calling prescribers if the prescriptions are submitted along with the correct form and meet the prior authorization criteria. The committee directed the PEC to post the prior authorization fax forms (instead of the prior authorization criteria) on the PEC website. Sufficient explanation and directions will be provided on the website to enable prescribers to fill out the fax form correctly and to emphasize that the forms are intended to facilitate sending prescriptions to the NMOP program only, not to the retail network.

C. Report on starter packs—MTFs may accept starter packs from pharmaceutical companies to the extent that the price paid for a drug includes the cost of any starter packs that are supplied by the pharmaceutical company. Present and future contracts (and DAPAs until they are deleted) should be reviewed to ensure they incorporate language to the effect that the prices charged for the drugs shall include the cost of any starter packs which may be distributed to DoD facilities and given to patients. The DOD Pharmacy Board of Directors recommended that MTFs determine local policy for the use of starter packs, with the caveat that starter packs should be dispensed by the pharmacy and not in the physician's office.

D. Report of the formulary management subcommittee—COL Remund reported that the task originally assigned to the subcommittee will be performed by a workgroup formed by TMA to draft regulations pertaining to the pharmacy benefit section of the FY 00 Defense Authorization Act. The subcommittee was dissolved.

E. Report of the fertility drugs subcommittee—This issue was tabled pending resolution of formulary redesign issues.

F. Report of the weight reduction subcommittee—TRICARE policy currently excludes coverage of drug therapy for weight reduction. MAJ Barb Roach (PEC) reported that a review of drug therapy for weight reduction did not reveal a compelling clinical imperative to recommend coverage for such therapy. The committee decided not to recommend any change to the TRICARE policy.

G. Advances in Medical Practice (AMP) funding initiative—A subcommittee was to have developed a list of drugs that could possibly be purchased with AMP funds, but officials responsible for the AMP program needed the list before the subcommittee could meet. The PEC gave the AMP officials a list of newly approved drugs that were categorized as to their relative clinical importance based on the degree of therapeutic advance over other agents, the severity/intractability of the condition, and the availability of other agents. The AMP officials will use this list to help determine which drugs should be obtained with AMP funding.

H. Status of TRICARE/CHAMPUS Policy Manual changes pertaining to pharmacy —CAPT Hostettler reported that Chapter 7 of the TRICARE/CHAMPUS Policy Manual has officially been changed so that quantity limits and prior authorizations apply uniformly to the NMOP and retail pharmacy networks.

6. NEW BUSINESS

A. Quantity Limits—MAJ Bellemin reported on quantity limits issues that were pending from the last meeting:

Blood product/biotech products: The committee decided that quantity limits on antihemophilic factors (e.g., Factor VIII, Factor IX Complex) were unnecessary, given the small number of prescriptions received by the NMOP for these agents. MAJ Bellemin informed the committee that the NMOP has quantity limits for other agents in this category that were not included on the list that the committee approved at the August 1999 meeting.

Topicals: Information regarding the typical quantities dispensed for five high-cost topicals (imiquimod (Aldara); calcipotriene (Dovonex); altitretinoin (Panretin); becaplermin (Regranex); and tazarotene (Tazorac)) is not yet available from Merck-Medco. Mark Petruzzi (Merck-Medco) will supply this information to a subcommittee consisting of Bill Hudson (Humana; subcommittee chair), MAJ George Jones, and all Managed Care Support Contractor (MCSC) pharmacy representatives. The subcommittee will formulate recommendations for quantity limits for these topical agents. An interim report is due to the co-chairs not later than 20 January 2000, and a full report is to be submitted to the committee at the next meeting. MAJ Bellemin informed the committee that the NMOP has quantity limits for other topicals that were not included on the list that the committee approved at the August 1999 meeting.

Antibiotics: MAJ Bellemin reported no problems with the current quantity limits on antibiotics. MAJ Bellemin also informed the committee that the NMOP has quantity limits for other antibiotics that were not included in the list that the committee approved at the August 1999 meeting.

Fertility Agents: MAJ Bellemin reported no problems or patient complaints associated with the 20 ampules per prescription quantity limit on injectable fertility agents.

Ophthalmics: MAJ Bellemin reported no problems with quantity limits on ophthalmics established at the last meeting.

Ondansetron for hyperemesis gravidarum: The quantity limits for ondansetron do not support the use of ondansetron for hyperemesis gravidarum. Ondansetron is Pregnancy Category B and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Consultation with MTF specialists indicated that ondansetron is not widely used or recommended for hyperemesis gravidarum. However, Gene Lakey (TriWest) reported that second level medical review through TriWest concluded that ondansetron is appropriate for hyperemesis gravidarum for some patients. The typical procedure in the retail network is to override the quantity limit if the medical review determines that a larger quantity is medically appropriate. The committee decided not to change the quantity limit for ondansetron in either the NMOP or the retail network because the small number of cases where ondansetron is used for hyperemesis gravidarum can be managed on an exception basis.

Actions: MAJ Bellemin and Mark Petruzzi (Merck-Medco) will supply a list of all NMOP quantity limits to the PEC. The PEC will then update the quantity limits listed on the PEC website. The PEC will submit a comprehensive list of all quantity limits for the NMOP and retail pharmacy networks for the committee to review at the next meeting.

B. Prior authorization for oral antifungal medications (NMOP and retail network)—TMA officials asked the committee to render an opinion about prior authorization criteria that attempt to differentiate between cosmetic and non-cosmetic use of oral terbinafine (Lamisil) for onychomycosis. COL Jeffery Meffert, MC, BAMC Dermatology, assisted the committee as a guest expert. After extensive discussion, the committee reached general agreement on the following points:

- It is difficult to clearly define and accurately differentiate cosmetic use from non-cosmetic use of oral terbinafine.
- Systemic antifungal therapy should not be instituted unless the presence of a fungal infection is clearly established by KOH prep, culture, or PAS stain. Use of systemic antifungal therapy in the absence of a fungal infection unnecessarily exposes the patient to the risk of adverse effects and wastes money.
- The pulse dosing of terbinafine for the treatment of onychomycosis provides the same degree of effectiveness and offers significant economic advantage over daily dosing.
- Even though the initial treatment with oral terbinafine usually eliminates the fungal infection, the nails may remain discolored until they grow out. It is inappropriate to continue oral terbinafine therapy just because the nails are discolored.

- A prior authorization program for oral terbinafine could potentially shift usage to itraconazole, which is even more expensive than terbinafine for onychomycosis.

The committee concluded that oral terbinafine should be subject to prior authorization that focuses on the appropriate diagnosis of onychomycosis and appropriate duration of therapy. The committee co-chairs will finalize the prior authorization criteria for oral terbinafine. The prior authorization program for oral terbinafine will be monitored for a shift in usage to the more expensive agent.

C. The committee considered a number of drugs for addition to the BCF and the NMOP Formulary. See Appendix A for a list of formulary changes.

D. Prior authorization for growth hormone treatment — The committee decided that in light of the costs associated with growth hormone treatment and the potential for inappropriate use, a subcommittee should evaluate the need for prior authorization and recommend appropriate criteria. The subcommittee will be chaired by Bill Hudson (Humana) and includes MAJ George Jones, MAJ Mickey Bellemin, Ray Nan Berry (Foundation Health), Kirby Davis (Anthem Alliance), William Hudson (Humana), Gene Lakey (TriWest), and Ron McDonald (Sierra Military Health Services). The subcommittee will evaluate current utilization in the NMOP and retail networks, formulate potential prior authorization criteria, and estimate potential cost savings associated with a prior authorization program. The subcommittee will submit an interim report to the co-chairs not later than 20 January 2000 and will provide the finalized report and recommendations to the committee at the next meeting.

E. Oral inhaled corticosteroids—On 1 November 1999 the price of the Schering brand of beclomethasone inhaler (Vanceril) increased from $5.75 to $19.27, and the price of the double strength beclomethasone inhaler (Vanceril DS) increased from $6.90 to $27.02. The committee decided to remove beclomethasone and beclomethasone double strength oral inhaler from the BCF because they are now among the most costly inhalers for any given dosage range (see Appendix C).

Although the triamcinolone oral inhaler is now the only oral corticosteroid inhaler remaining on the BCF, that does not mean that MTFs should have only the triamcinolone inhaler on their formularies. MTFs almost certainly need more than one oral corticosteroid to satisfy the clinical needs of patients, but the committee did not want to mandate a specific inhaler by selecting another inhaler for the BCF. Price instability within the drug class, the anticipated introduction of products reformulated without chlorofluorocarbons, and the impending introduction of a new agent make it difficult for the committee to ascertain which inhaler (in addition to triamcinolone) provides the greatest value. The committee recommends that MTFs consider the information provided in Appendix C in selecting agents for MTF formularies.

F. Selective serotonin reuptake inhibitors—The BCF currently specifies that MTFs must have at least one SSRI on their formularies, but the BCF does not identify a specific SSRI. The committee considered two options regarding the status of SSRIs on the BCF:

- Option 1: Add citalopram, fluoxetine, paroxetine, and sertraline to the BCF and provide information that the MTFs and/or TRICARE regions could use to encourage greater use of the more cost-effective agents.

- Option 2: Continue the current status of SSRIs on the BCF and provide information that the MTFs and/or TRICARE regions could use to encourage greater use of the most cost-effective agents.

The committee selected Option 2 because of concern that Option 1 would cause large increases in expenditures for SSRIs at MTFs that currently have only one SSRI on formulary. The BCF will continue to specify that MTFs must have at least one SSRI on their formularies. The committee directed the PEC to provide information about the relative cost-effectiveness of the SSRIs to MTFs and TRICARE regions. The committee strongly encourages MTFs and TRICARE regions to maximize the use of the most cost-effective SSRIs when consistent with the clinical needs of patients.

G. Withdrawal of betaxolol (Betoptic; Alcon) ophthalmic solution—The committee approved a change in the BCF listing for "betaxolol ophthalmic solution" to "betaxolol ophthalmic suspension" as a result of the withdrawal of betaxolol ophthalmic solution from the market. Betaxolol ophthalmic suspension (Betoptic S; Alcon) remains available. Another ophthalmic beta-blocker, timolol, is also on the BCF.

H. Unavailability of propranolol LA —Mel Miller (PEC) informed the committee that Wyeth-Ayerst sent a letter to physicians and patients concerning an anticipated shortage of both Inderal LA and generic propranolol LA, both of which are made by Wyeth-Ayerst. The committee concluded that this is probably not a significant issue for DoD because propranolol LA (brand and generic) accounts for a relatively small proportion of oral beta-blockers used by DoD facilities. Additionally, Wyeth-Ayerst has notified its customers that it will be shipping product by mid-December, so any shortages will be short-lived.

I. Legislation regarding the DoD P&T Committee and DoD formulary management—Capt Hostettler and Mr. Altschwager briefed the committee on the FY00 Defense Authorization Act that amends Chapter 55 of title 10, United States Code, to establish a DoD Pharmacy Benefits Program. The Pharmacy Benefits Program provides for the establishment of a uniform formulary, a DoD P&T Committee, and a Uniform Formulary Beneficiary Advisory Panel that will review and comment on the development of the uniform formulary and subsequent formulary changes.

J. Pharmaceutical contracts awarded since last P&T meeting—COL Remund reported that DoD statin contracts were awarded to Merck for simvastatin (Zocor) and to Bayer for cerivastatin (Baycol). These contracts “close” the statin class on the BCF. A joint DoD-VA contract was awarded to Novo Nordisk for 10 mL vials of human insulin (rDNA) N, R, L, and 70/30. Joint DoD-VA generic contracts were awarded for specific brands of amantadine capsules, amoxicillin capsules, captopril tablets, fluocinolone solution, fluocinonide cream, fluocinonide ointment, fluocinonide solution, nortriptyline capsules, prazosin capsules, and verapamil sustained-release tablets. A summary of national pharmaceutical contracts is provided in Appendix D.

K. DoD P&T Committee involvement in pharmaceutical procurement contracts—Any pharmaceutical contracting initiative that is more complex than the simple selection of a specific brand among AB-rated generics should be sanctioned by the DoD P&T Committee

before a solicitation is issued.

L. Potential contracting initiatives:

1. *Estrogen replacement therapy:* Conjugated estrogen (Premarin) is on the BCF and has more than 90% of the estrogen replacement therapy market in DoD. The current price for Premarin tablets is nearly triple the price that existed when the drug was in the depot system. Alternate drugs are available to compete for market share. For example, a large HMO in the state of Washington achieved significant cost savings by converting more than 14,000 patients from conjugated estrogens to an esterified estrogen product. The committee recommended that DSCP and the PEC continue to explore the potential for a joint VA and DoD contract. The committee also recommended that DSCP explore potential price reductions through DAPA incentive agreements.

2. *Nicotine patches:* The joint DoD/VA clinical practice guideline for smoking cessation includes the use of nicotine patches. Drug therapy for smoking cessation is not a covered benefit in the NMOP and retail pharmacy networks. A nicotine patch is not listed on the BCF, but some MTFs provide nicotine patches as part of smoking cessation programs. The 3-step (21 mg, 14 mg, and 7 mg) nicotine patches account for the vast majority of DoD and VA nicotine patch usage. Four companies market a 3-step nicotine patch, so an opportunity exists for price competition. The committee favors a contracting initiative that will lower the cost of nicotine patches for those MTFs that choose to have a nicotine patch on their formulary. The committee, however, does not want to select a nicotine patch for the BCF and thus mandate that all MTFs have a nicotine patch on their formularies. The committee recommended that VA and DoD seek a joint contract for a single brand of 3-step nicotine patches. The committee recommended that the contract include the following provisions:

   - The contract would not require MTFs to have a nicotine patch on their formularies. If an MTF does have a 3-step nicotine patch on its formulary, it must be the contracted brand. An MTF may not have a non-contracted brand of 3-step nicotine patches on its formulary.

   - The nicotine patch class would remain "open" on the BCF. The contract would not affect the formulary status of other types of nicotine patches (i.e. 1-step (Nicotrol) or 2-step (Prostep) patches). MTFs could choose to have Nicotrol or Prostep patches on their formularies in addition to or instead of the contracted brand of the 3-step nicotine patch.

3. *Non-sedating antihistamines:* DoD expenditures are increasing significantly in this drug class. None of the agents are on the BCF. The following issues affect the potential for a joint contract for VA and DoD in this drug class:

   - Some MTFs oppose a contract that would add a non-sedating antihistamine to the BCF because they do not want to add a non-sedating antihistamine to the MTF formulary.

   - Some MTFs want a contract that adds a non-sedating antihistamine to the BCF in order to obtain significant price reductions.

- Definition of the drug class is problematic. Loratidine (Claritin) and fexofenadine (Allegra) are classified as “non-sedating” antihistamines. Cetirizine (Zyrtec) is considered a “low-sedating” antihistamine since the incidence of sedation in clinical trials with cetirizine is significantly more than with placebo. All three agents appear to be less sedating than conventional antihistamines.

The committee recommended that VA and DoD explore the possibility of a joint contract that would select a non-sedating antihistamine for the BCF and leave the class “open” on the BCF. The committee also recommended that DSCP should seek price reductions through DAPA incentive agreements.

7. ADJOURNMENT: The meeting adjourned at 1500 hours. The next meeting will be held on Thursday, 24 February 2000, at Portsmouth, Virginia. All agenda items should be submitted to the DoD PEC no later than Friday, 28 January 2000.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL,MS,USA	CDR, MC,USN
Co-chairman	Co-chairman

LIST OF APPENDICES:

Appendix A: Formulary Changes

Appendix B: Reports Due to the Committee

Appendix C: Table: Cost per Month for Oral Inhaled Corticosteroids (Adults)

Appendix D: Table: DoD and DoD/VA Pharmaceutical Contracts

Appendix A: Formulary Changes

A. BCF

1. Beclomethasone and beclomethasone double strength oral inhalers were removed from the BCF.

2. The BCF listing for betaxolol ophthalmic solution was changed to betaxolol ophthalmic suspension as a result of the withdrawal of the solution formulation.

B. NMOP

1. Ketotifen fumarate ophthalmic solution (Zaditor; Ciba Vision) —added to NMOP Formulary

2. Pioglitazone (Actos; Takeda) —added to NMOP Formulary

3. Temozolomide (Temodar; Schering) —Bill Hudson (Humana) reported that pharmacies in national chains, which tend to have their own warehouses and distribution systems, have reported some trouble obtaining this drug, since the national chains have not been stocking this in their warehouses. Although the committee agreed that the NMOP is probably not the most efficient or desirable way for patients to acquire this chemotherapy agent, the committee agreed that temozolomide should be available through the NMOP. Added to the NMOP Formulary with a 30-day quantity limit (1 cycle).

4. Zaleplon (Sonata; Wyeth-Ayerst) —added to NMOP Formulary with a 30-day quantity limit due to its status as a Schedule IV drug as well as recommendations in product labeling

5. Doxercalciferol (Hectorol; Bone Care International) —added to NMOP Formulary

6. Cyanocobalamin intranasal gel (Nascobal; Schwarz Pharma) —The current excluded drug listing on the NMOP Formulary reads "Legend vitamins - Please note that legend formulations of folic acid, niacin, and vitamins D, K, and B12 (injection) are covered." The intranasal formulation of cyanocobalamin is an alternative for treatment of B12 deficiency states (in patients who are hematologically stable and do not have nervous system involvement). The committee agreed to change the excluded drug list notation to "Legend vitamins - Please note that legend formulations of folic acid, niacin, and vitamins D, K, and B12 are covered" and notify Merck-Medco that intranasal cyanocobalamin gel is covered.

7. Sermorelin acetate for injection (Geref; Serono) —This agent is growth hormone releasing hormone, indicated for treatment of idiopathic growth hormone deficiency in children with growth failure. It is useful only in children who retain pituitary responsiveness to growth hormone releasing hormone. Other growth hormone products are currently on the NMOP Formulary. Unlike the growth hormones, growth hormone-releasing hormone may be undetectable by current testing for growth hormone use in athletic competitions.

Added to NMOP Formulary only for patients who are 16 years old or younger. Mark Petruzzi (Merck-Medco) will report back to committee co-chairs if there are any problems with implementing the age edit in the NMOP.

8. Levonorgestrel tablets (Plan B; Women's Capital Corporation) —This emergency contraception product was excluded from the NMOP Formulary because it must be used within 72 hours of unprotected intercourse to be effective.

9. Rabeprazole (Aciphex; Eisai/Janssen) —excluded from the NMOP Formulary per contractual requirements of the proton pump inhibitor contract. Like lansoprazole (Prevacid; TAP), rabeprazole will be listed as a "non-contracted drug" on the NMOP Formulary. It will be provided by the NMOP only if medical necessity is substantiated.

10. Entacapone (Comtan; Orion/Novartis) —added to NMOP Formulary

11. Sirolimus solution (Rapamune; Wyeth Ayerst) —added to NMOP Formulary

12. Zileuton (Zyflo; Abbott) was removed from the list of non-preferred drugs.

Appendix B: Reports Due to the Committee

1. Growth hormone subcommittee (Bill Hudson (chair); MAJ George Jones; MAJ Mickey Bellemin; Ray Nan Berry (Foundation Health); Kirby Davis (Anthem Alliance); William Hudson (Humana); Gene Lakey (TriWest); Ron McDonald (Sierra Military Health Services)) — An interim report is due to the co-chairs not later than 20 January 2000, and a full report with recommendations is due at the next meeting of the P&T committee.

2. Listing of quantity limits on the PEC website — MAJ Bellemin and Mark Petruzzi (Merck-Medco) will supply a list of all NMOP quantity limits to the PEC. The PEC will then update its website to accurately reflect quantity limits for blood products/biotech products, antibiotics, topicals and other categories as necessary. The PEC will submit a complete report of all quantity limits for the NMOP and retail pharmacy networks for the committee to review at the next meeting.

3. Quantity limits for topicals — A subcommittee consisting of Bill Hudson (chair); MAJ George Jones; MAJ Mickey Bellemin; Ray Nan Berry (Foundation Health); Kirby Davis (Anthem Alliance); William Hudson (Humana); Gene Lakey (TriWest); and Ron McDonald (Sierra Military Health Services) will formulate recommendations for quantity limits on five high-cost topicals: imiquimod (Aldara); calcipotriene (Dovonex); altitretinoin (Panretin); becaplermin (Regranex); and tazarotene (Tazorac).

4. Non-preferred/preferred drug pairs standard report (see Paragraph 5A3) — CDR Brouker (PEC) will submit a draft of a standard report to the co-chairs not later than 17 December 1999. CDR Brouker will submit the finalized version of the report to the committee at the next meeting.

5. Prior authorization for oral antifungals — CDR Terry Egland, COL Dan Remund will report the status of the prior authorization for oral terbinafine at the next meeting.

Appendix C: Cost per month for oral inhaled corticosteroids (adults)

						Number of puffs per day and approximate cost per month		
NDC	**Generic Name**	**Trade Name**	**Pkg sz**	**# Inh per unit**	**DAPA 10/99***	**Low dose****	**Medium dose****	**High dose****
173046900	Beclomethasone 42mcg/puff	Beclovent (Glaxo) MDI	6.7 GM	80	8.00	4 - 12 puffs $12.00 - $36.00	12 - 20 puffs $36.00 - $60.00	20 or more puffs $60.00 +
173031288	Beclomethasone 42mcg/puff	Beclovent (Glaxo) MDI	16.8 GM	200	19.07	4 - 12 puffs $11.44 - $34.33	12 - 20 puffs $34.33- $57.21	20 or more puffs $57.21 +
85111201	Beclomethasone 84mcg/Actuat	Vanceril-DS (Schering) MDI	12.2 GM	120	27.02	2 - 6 puffs $13.51 - $40.53	6 - 10 puffs $40.53 - $67.55	10 or more puffs $67.55 +
85073604	Beclomethasone 42mcg/puff	Vanceril (Schering) MDI	17 GM	200	19.27	4 - 12 puffs $11.56 - $34.69	12 - 20 puffs $34.69- $57.81	20 or more puffs $57.81+
186091542	Budesonide 200mcg/Inhl	Pulmicort (Astra) DPI	0.4 GM	200	67.42	1 - 2 puffs $10.11 - 20.23	2 - 3 puffs $20.23 - $30.34	3 - 4 or more puffs $30.34 - 40.45 +
456067099	Flunisolide 250mcg/puff Menthol	Aerobid-M (Forest) MDI	7 GM	100	2.79	2 - 4 puffs $1.67- $3.35	4 - 8 puffs $3.35 - $6.70	8 or more puffs $6.70 +
456067299	Flunisolide 250mcg/puff	Aerobid (Forest) MDI	7 GM	100	2.79	2 - 4 puffs $1.67- $3.35	4 - 8 puffs $3.35 - $6.70	8 or more puffs $6.70 +
173049700	Fluticasone 44mcg/puff	Flovent (Glaxo) MDI	7.9 GM	60	19.64	2 - 6 puffs $19.64- $58.92		
173049100	Fluticasone 44mcg/puff	Flovent (Glaxo) MDI	13 GM	120	13.78	2 - 6 puffs $6.89 - $20.67		
173049800	Fluticasone 110mcg/puff	Flovent (Glaxo) MDI	7.9 GM	60	24.57	2 puffs $24.57	2 - 6 puffs $24.57 - $73.71	6 - 8 puffs $73.71- $98.28
173049400	Fluticasone 110mcg/puff	Flovent (Glaxo) MDI	13 GM	120	21.95	2 puffs $10.98	2 - 6 puffs $10.98 - $32.93	6 - 8 puffs $32.93 - $43.90
173049900	Fluticasone 220mcg/puff	Flovent (Glaxo) MDI	7.9 GM	60	38.53			3 - 4 puffs $57.80 - $77.06
173049500	Fluticasone 220mcg/puff	Flovent (Glaxo) MDI	13 GM	120	45.97			3 - 4 puffs $34.48 - $45.97
173051100	Fluticasone 50 Mcg/Inhalation	Flovent Rotadisk (Glaxo) DPI	1.5 GM	60	12.95	2 - 6 puffs $12.95 - $38.85		
173050900	Fluticasone 100 Mcg/Inhalation	Flovent Rotadisk (Glaxo) DPI	1.5 GM	60	14.5		3 - 6 puffs $21.75 - $43.50	6 - 10 puffs $43.50- $72.50
173050400	Fluticasone 250 Mcg/Inhalation	Flovent Rotadisk (Glaxo) DPI	1.5 GM	60	34.73			2 - 4 puffs $34.73- $69.46
75006037	Triamcinolone 100mcg/puff	Azmacort (RPR) MDI	20 GM	240	9.6	4 - 8 puffs $4.80 - $9.60	8 - 12 puffs $9.60 - $14.40	12 - 16 puffs $14.40 - $19.20

* DAPA price for a 30-day supply as of 10/1/99 plus Schering price increases effective 11/1/99

** Dose in puffs or inhalations/day, derived from NHLBI Asthma Guidelines--Expert Panel 2 Report Figure 3-5b, page 88

Appendix D: DoD and DoD/VA Pharmaceutical Contracts

Drug	Manufacturer	Strength	NDC	Package Size	Package Cost	Tablet or Capsule Cost	Contract Base Period*	Potential Annual Cost Avoidance
Albuterol inhaler	Warrick	0.09 mg/ inh	59930-1560-01	17 gm	$1.75	NA	11/98-11/99	$568,000
Amantadine capsules	Invamed	100 mg	62269-0211-24 62269-0211-29	100 500	$5.50 $26.00	$0.0550 $0.0520	8/99-8/00	$16,000†
Amoxicillin capsules	Apothecon	250 mg	00003-0101-50 00003-0101-60	100 500	$2.65 $10.87	$0.0260 $0.0220	8/99-8/00	$69,121
		500 mg	00003-0109-55 00003-0109-60	100 500	$4.50 $18.99	$0.0450 $0.0380		
Captopril tablets	Apothecon	12.5 mg	59772-7045-01 59772-7045-03	100 1000	$1.17 $9.24	$0.0117 $0.0092	10/99-10/00	$230,000
		25 mg	59772-7046-01 59772-7046-03	100 1000	$1.25 $10.77	$0.0125 $0.0108		
		50 mg	59772-7047-01 59772-7047-03	100 1000	$2.10 $16.50	$0.0210 $0.0165		
		100 mg	59772-7048-01	100	$5.14	$0.0514		
Cerivastatin	Bayer	0.2 mg	00026-2883-51	100	$30.00	$0.3000	8/99-8/00	See Simvastatin
		0.3 mg	00026-2884-51	100	$30.00	$0.3000		
		0.4 mg	00026-2885-69 00026-2885-51	30 100	$9.00 $30.00	$0.3000 $0.3000		
Cimetidine	Sidmak	300 mg	50111-550-01 50111-550-02 50111-550-03	100 500 1000	$3.12 $14.20 $27.56	$0.0312 $0.0284 $0.0276	11/98-11/99	$300,000‡
		400 mg	50111-551-04 50111-551-01 50111-551-02 50111-551-03	60 100 500 1000	$2.72 $4.04 $18.40 $34.40	$0.0453 $0.0404 $0.0368 $0.0344		
		800 mg	50111-552-10 50111-552-01 50111-552-02	30 100 500	$2.68 $8.90 $42.25	$0.0893 $0.0890 $0.0845		
Diltiazem extended release tablets	Forest	120 mg	00456-2612-00 00456-2612-30 00456-2612-90	1000 30 90	$270.00 $8.10 $24.30	$0.2700 $0.2700 $0.2700	12/98-12/99	$5.7 million
		180 mg	00456-2613-00 00456-2613-30 00456-2613-90	1000 30 90	$270.00 $8.10 $24.30	$0.2700 $0.2700 $0.2700		
		240 mg	00456-2614-00 00456-2614-30 00456-2614-90	1000 30 90	$270.00 $8.10 $24.30	$0.2700 $0.2700 $0.2700		
		300 mg	00456-2615-00 00456-2615-30 00456-2615-90	1000 30 90	$430.00 $12.90 $38.70	$0.4300 $0.4300 $0.4300		
		360 mg	00456-2616-00 00456-2616-30 00456-2616-90	1000 30 90	$430.00 $12.90 $38.70	$0.4300 $0.4300 $0.4300		
Fluocinolone solution	Bausch & Lomb	0.01%	24208-0465-63 24208-0465-67	20 ml 60 ml	$1.72 $2.12	NA	9/99-9/00	Not significant
Fluocinonide cream	Teva	0.05%	00093-0262-15 00093-0262-30 00093-0262-92	15 gm 30 gm 60 gm	$1.00 $1.50 $2.25	NA	9/99-9/00	$288,000
Fluocinonide ointment	Teva	0.05%	00093-0264-15 00093-0264-30 00093-0264-92	15 gm 30 gm 60 gm	$3.50 $5.50 $7.25	NA		
Fluocinonide soln	Teva	0.05%	00093-0266-39	60 ml	$5.50	NA		
Lisinopril tablets	Zeneca	2.5 mg	00310-0135-10	100	$14.00	$0.1400	8/99-8/00	$7.6 million
		5 mg	00310-0130-39 00310-0130-10 00310-0130-34	100 UD 100 1000	$14.00 $14.00 $140.00	$0.1400 $0.1400 $0.1400		
		10 mg	00310-0131-39 00310-0131-10 00310-0131-34 00310-0131-73	100 UD 100 1000 3000	$14.00 $14.00 $140.00 $420.00	$0.1400 $0.1400 $0.1400 $0.1400		
		20 mg	00310-0132-39 00310-0132-10 00310-0132-34 00310-0132-73	100 UD 100 1000 3000	$14.00 $14.00 $140.00 $420.00	$0.1400 $0.1400 $0.1400 $0.1400		
		40 mg	00310-0134-10	100	$14.00	$0.1400		

* Most contracts have options for renewal periods
† Estimate ranges from $15,500 to $17,500 depending on purchased package size mix
‡ Estimate ranges from $233,000 to $364,000

Appendix D (continued): DoD and DoD/VA Pharmaceutical Contracts

Drug	Manufacturer	Strength	NDC	Package Size	Package Cost	Tablet or Capsule Cost	Contract Base Period*	Potential Annual Cost Avoidance
Insulin, Human (rDNA)	Novo Nordisk	Novolin N	00169-1834-11	10 ML	$4.49	NA	11/99-11/00	$820,000
		Novolin R	00169-1833-11	10 ML	$4.49			
		Novolin L	00169-1835-11	10 ML	$4.49			
		Novolin 70/30	00169-1837-11	10 ML	$4.49			
Nortriptyline capsules	Teva	10 mg	00093-0810-01	100	$1.83	$0.0183	10/99-10/00	$179,000
			00093-0810-05	500	$8.69	$0.0174		
		25 mg	00093-0811-01	100	$2.46	$0.0246		
			00093-0811-05	500	$11.07	$0.0221		
		50 mg	00093-0812-01	100	$3.31	$0.0331		
			00093-0812-05	500	$15.72	$0.0314		
		75 mg	00093-0813-01	100	$4.21	$0.0421		
Omeprazole capsules	Astra	10 mg	00186-0606-28	100 UD	$140.00	$1.4000	10/99-10/00	$11.6 million
			00186-0606-31	30	$42.00	$1.4000		
			00186-0606-68	100	$75.93	$0.7593		
			61113-0606-82	1000	$$1,400.00	$1.4000		
		20 mg	61113-0742-28	100 UD	$140.00	$1.4000		
			00186-0742-31	30	$42.00	$1.4000		
			00186-0742-82	1000	$1,400.00	$1.4000		
		40 mg	61113-0743-28	100 UD	$140.00	$1.4000		
			61113-0743-31	30	$42.00	$1.4000		
			61113-0743-68	100	$140.00	$1.4000		
			61113-0743-82	1000	$1,400.00	$1.4000		
Prazosin capsules	Zenith Goldline	1 mg	00172-4067-60	100	$1.90	$0.0190	11/99-11/00	$53,000
			00172-4067-80	1000	$19.00	$0.0190		
		2 mg	00172-4068-60	100	$2.50	$0.0250		
			00172-4068-80	1000	$25.00	$0.0250		
		5 mg	00172-4069-60	100	$4.02	$0.0402		
			00172-4069-70	500	$21.20			
Ranitidine tablets	Geneva	150 mg	00781-1883-60	60	$1.93	$0.0320	12/98-12/99	$4,493,000§
			00781-1883-05	500	$13.57	$0.0270		
			00781-1883-10	1000	$26.72	$0.0270		
		300 mg	00781-1884-31	30	$2.28	$0.0760		
			00781-1884-25	250	$16.48	$0.0660		
Simvastatin tablets	Merck	5 mg	00006-0726-61	60	$27.00	$0.4500	8/99-8/00	$22.2 million in combination with Cerivastatin
			00006-0726-54	90	$40.50	$0.4500		
			00006-0726-28	100 UD	$45.00	$0.4500		
		10 mg	00006-0735-61	60	$39.60	$0.6600		
			00006-0735-54	90	$59.40	$0.6600		
			00006-0735-28	100 UD	$66.00	$0.6600		
			00006-0735-82	1000	$660.00	$0.6600		
			00006-0735-87	10,000	$6,600.00	$0.6600		
		20 mg	00006-0740-61	60	$64.20	$1.0700		
			00006-0740-28	100 UD	$107.00	$1.0700		
			00006-0740-82	1000	$1,070.00	$1.0700		
			00006-0740-87	10,000	$10,700.00	$1.0700		
		40 mg	00006-0749-61	60	$64.20	$1.0700		
		80 mg	00006-0543-61	60	$64.20	$1.0700		
Verapamil sustained-release tablets	Zenith Goldline°	120 mg	00172-4285-60	100	$12.99	$0.1299	12/99-11/00	To be determined
		180 mg	00172-4286-60	100	$5.97	$0.0597		
		240 mg	00172-4280-60	100	$5.97	$0.0597		
			00172-4280-70	500	$29.00	$0.0580		

* Most contracts have options for renewal periods

§ Estimated cost avoidance for ranitidine ranges from $765,000 (based on lowest available DAPA price at time of award) to $7,321,000 (based on actual purchases for FY98). The $4,493,000 estimate is based on the DAPA price of the Geneva brand that existed prior to the award of the contract.

° Contract was previously awarded to G.D.Searle, with a base contract performance period of 8/20/99-8/19/00. After the contract was awarded, G.D. Searle stated that they had made a mistake on the price of the 240 mg 500s ($9.50/bottle of 500). The contract will be terminated on 12/1/99. A settlement has been reached concerning the price of the 240mg bottle of 500 during the period of time the contract was in effect.

Department of Defense
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MCCS-GPE 30 August 1999

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 13 August 1999, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, TX.

2. MEMBERS PRESENT:

COL Daniel D. Remund, MS	Co-chairman
CDR Terrance Egland, MC	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Danielle Doyle	Army
CDR Matt Nutaitis, MC	Navy
LCDR Kevin Cook	Navy
LTC John R. Downs, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard
Ronald L. Mosier	Department of Veterans Affairs (alternate)
LTC (P) George Crawford, MS	Joint Readiness Clinical Advisory Board
LTC Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin BSC	Defense Supply Center Philadelphia (DSCP)
C. Andrew Bergman	Uniformed Services Family Health Plans (USFHP)
Ray Nan Berry	Foundation Health
Kirby Davis	Anthem Alliance
William Hudson	Humana, Inc
Gene Lakey	TriWest
Ron McDonald	Sierra Military Health Services

3. OTHERS PRESENT:

CAPT Charlie Hostettler, MSC	DoD Pharmacy Program Director, TMA
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
MAJ Donald DeGroff	DoD Pharmacoeconomic Center
LCDR Mark Richerson	DoD Pharmacoeconomic Center
MAJ Barbara Roach	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Tom Kellenberger	Merck-Medco
Mark Petruzzi	Merck-Medco
Shelby Tanner, Jr.	Staff Judge Advocate, Fort Sam Houston
David Chicoine	Uniformed Services Family Health Plans (USFHP)

4. ADMINISTRATIVE ISSUES:

A. Financial disclosure reports were distributed to voting members of the committee and alternates. Voting members and alternates are to return the reports to COL Remund not later than the next meeting.

B. Introduction of new members and attendees: LCDR Kevin Cook replaced LCDR Denise Graham as a Navy representative. C. Andrew Bergman, MD, Johns Hopkins Medical Services Corporation is a new committee member representing the Uniformed Services Family Health Plans (USFHP). David Chicoine, Administrative Director, Brighton Marine Health Center also attended the meeting on behalf of the USFHP. The USFHP is a Department of Defense-sponsored managed healthcare option currently providing care to nearly 100,000 eligible family members of active duty personnel, retirees and their families in seven areas of the country.

C. The minutes from the 14 May 99 meeting were accepted as written.

5. OLD BUSINESS:

A. CDR Mark Brouker, Deputy Director of the Pharmacoeconomic Center (PEC), compared the estimated cost avoidance and phone call workload for the old NMOP preferred drug list (PDL) to the current non-preferred/preferred drugs on the restructured NMOP formulary. Based on data for a 10-week period (see Table 1, Appendix A), each phone call requesting a change from a non-preferred agent to a preferred alternative under the restructured NMOP formulary results in a $30 cost avoidance, compared to only $7 under the old NMOP PDL. DoD annual cost avoidance is projected to increase from $171,000 to $588,000. Phone calls to request switches have decreased from 2% to 1.6% of total prescriptions filled.

The Committee approved a PEC proposal to add four pairs of non-preferred/preferred drugs to the NMOP formulary (see table below). These non-preferred/preferred drugs are projected to yield an average cost avoidance of $58 per phone call and $397,000 in annual cost avoidance (see Table 2, Appendix A). A summary of the cost avoidance and phone call workload estimates is provided in Table 3, Appendix A.

Additional Non-Preferred/Preferred Drugs on NMOP Formulary

Non-Preferred Drug	**Preferred Alternative**
famotidine (Pepcid)	ranitidine (Geneva brand generic*)
nizatidine (Axid)	ranitidine (Geneva brand generic*)
enalapril (Vasotec)	lisinopril (Zestril* brand)
nitroglycerin patches (Minitran, Transderm Nitro, Nitrodisc, and generics)	nitroglycerin patches (Nitro-Dur)
	* national contracts specify the brands of these preferred alternative drugs

The Committee removed astemizole (Hismanal) from the non-preferred/preferred alternative list due to its withdrawal from the market. Cartia XT (Andrx's generic equivalent for Cardizem CD) was added to the non-preferred listing for diltiazem extended-release.

B. CDR Brouker reported that the NMOP implemented prior authorization procedures for celecoxib (Celebrex) on 2 August 1999. Prior authorization procedures for etanercept (Enbrel) are being implemented as of 13 August 1999. Prior authorization procedures for sildenafil (Viagra), which is currently available through the NMOP, will be implemented no later than 24 Sep 99.

A subcommittee will attempt to quantify the value of the NMOP prior authorization program in terms of clinical, economic, and humanistic outcomes. Members of the subcommittee are: CDR Mark Brouker (PEC); MAJ Mickey Bellemin (DSCP), Tom Kellenberger and Mark Petruzzi (Merck-Medco). The subcommittee will report on its measurement efforts at the next meeting.

C. At the May 14 meeting, the committee voted to add over-the-counter (OTC) forms of niacin prescribed for antilipemic therapy to the list of OTC items that are covered by the NMOP. Implementation of this decision was contingent on a TMA policy review. TMA legal opinion is that this decision represents an improper application of discretionary authority because it waives a policy provision for a class of cases rather than for an individual case. Based on the TMA legal opinion, OTC forms of niacin will not be available through the NMOP. Prescription forms of niacin remain available through the NMOP.

D. MAJ Bellemin reported on the current status of disposable insulin syringes, alcohol swabs, blood glucose test strips, lancets, and disposable syringes for non-insulin injectable medications on the NMOP formulary:

1) Disposable Insulin Syringes and Alcohol Swabs are dispensed on one prescription number and require only one co-pay. A quantity of alcohol swabs equal to or rounded up to the nearest 100 of the quantity of syringes prescribed is automatically dispensed whenever a prescription for insulin syringes is received.

2) Blood glucose test strips and lancets are dispensed on one prescription number and require only one co-pay. A quantity of lancets equal to or rounded up to the nearest 100 of the quantity of blood test strips prescribed is automatically dispensed whenever a prescription for blood test strips is received.

3) Syringes will be provided through the NMOP if they are prescribed in conjunction with a prescription for an injectable medication. A separate prescription should be written for the syringes, and the prescription should specify the type of syringe. A quantity of alcohol swabs equal to or rounded up to the nearest 100 of the quantity of the corresponding syringes will be automatically dispensed. A co-pay will be required for the syringes/alcohol swabs in addition to the co-pay for the injectable medication.

E. The committee reviewed the current status of oral corticosteroid inhalers on the BCF. There have been no substantial price increases in this class since the last meeting. The committee agreed that there does not appear to be any reason to make changes to the BCF agents at this time. Vanceril, Vanceril DS, and Azmacort will remain on the BCF. The PEC will continue to monitor price changes in this class and will bring the issue back to the P&T committee if it needs to be revisited.

F. Instead of pursuing a sole source contract for warfarin sodium, the committee advised the Defense Supply Center Philadelphia to accept a DAPA incentive agreement that reduces the price of the Coumadin brand of warfarin sodium. The DAPA incentive agreement will yield approximately $700,000 annually in cost avoidance for DoD based on current DoD usage data for the Coumadin brand of warfarin. The DAPA incentive agreement will obviate the need for a formal contracting initiative, so DSCP can focus its efforts on drug classes with greater economic implications to DoD. The DAPA incentive agreement does not affect the BCF listing for warfarin. The BCF will continue to list warfarin with no brand name specified. MTFs may select any brand of warfarin for their local formularies. All currently marketed brands of warfarin are AB rated to the DuPont product.

6. NEW BUSINESS:

A. Contracting update

1. *Diltiazem extended release* – The DoD/VA contract awarded to Forest Pharmaceuticals for Tiazac as the mandatory sole source product for extended-release diltiazem was effective 15 Dec 98. COL Remund reported on the success of the contract implementation for Tiazac (see Appendix B). By the end of April 99, the last month for which complete prime vendor data is available, market share for Tiazac had exceeded 80%. The cumulative cost avoidance attributable to the contract was over $1 million through April 99. The annual cost avoidance to DoD from this contract is estimated to be $5.5 million dollars.

2. *Lisinopril* – A DoD contract awarded to Zeneca Pharmaceuticals for the Zestril brand of lisinopril took effect 1 Aug 99. All MTFs and the NMOP must use only the Zestril brand of Lisinopril. The contract does not close the ACE inhibitor class. The contract has no effect on the BCF status or MTF formulary status of ACE inhibitors other than lisinopril. The Zestril brand of lisinopril is now flat-priced at $0.14 per tablet for all strengths and package sizes. An annual cost avoidance of $7.5 million is projected for the lisinopril contract.

3. *Proton pump inhibitors (PPIs)* – A DoD contract for proton pump inhibitors was awarded to Astra Pharmaceuticals for omeprazole (Prilosec) on 6 August 99. The contract takes effect on 1 Oct 99 and closes the PPI class on the BCF. Omeprazole must be on all MTF formularies. No other PPI is permitted on any MTF formulary. PPIs other than omeprazole will not be available at MTF pharmacies or the NMOP, unless a medical necessity requires the use of a PPI other than omeprazole for an individual patient. An implementation plan for the PPI contract was sent out to all MTFs. The price per capsule for omeprazole decreased from $1.72 for most strengths to the contract price of $1.40 for all strengths and all package sizes except the 100-count bottles of omeprazole 10 mg. The 100-count package size of omeprazole 10-mg remains at its previous DAPA price of $0.76 per capsule due to federal ceiling price regulations. The price reductions are projected to yield $11.6 million annually in cost avoidance to DoD.

4. *Insulin* – LTC Rick Downs reported that the DoD/VA contract solicitation for insulin was issued 26 July 99 and closes 25 August 99.

5. *Statins* – COL Remund reported that the General Accounting Office (GAO) was expected to rule on two protests concerning the DoD contract solicitation for HMG-CoA reductase inhibitors (statins) no later than 18 August 99. If the GAO decides in favor of DoD, a contract award announcement may be made shortly thereafter.

B. CAPT Hostettler informed committee members about portions of the pending FY 2000 National Defense Authorization Bill that pertain to the DoD P&T Committee and formulary

management.

C. The committee approved a recommendation that a subcommittee be established to draft a set of principles to guide formulary management decisions. Subcommittee members are CDR Egland, MAJ George Jones, COL Remund, Bill Hudson, and Tom Kellenberger. A draft set of principles is to be presented at the next P&T committee meeting.

D. Per guidance from higher authority, the committee tabled a decision on the proposal to select one SSRI for the BCF while leaving the class open.

E. The committee approved the addition of spironolactone to the BCF. This decision was primarily in response to results from the RALES (Randomized Aldactone Evaluation Study) trial in patients with severe congestive heart failure. The trial was discontinued early because an interim analysis showed that the addition of low doses of spironolactone to standard therapy in patients with severe CHF was associated with a 30 percent reduction in mortality, a 30 percent reduction in cardiac hospitalizations, and significant improvements in New York Heart Association (NYHA) class. The results of the RALES trial are available in their entirety on the Internet at www.nejm.org, and will be published in the 2 Sep 99 issue of the *New England Journal of Medicine.*

   Spironolactone 25 mg is generically available from several manufacturers at DAPA prices ranging from $0.02 per tablet for the lowest priced generic to $0.25 per tablet for the brand-name product (Aldactone; Searle). At the lowest generic price, a year of therapy with spironolactone 25 mg daily would cost $8.00. The FDA recently approved a generic version of spironolactone 50- and 100-mg tablets.

F. Due to a substantial DAPA price increase, the committee removed beclomethasone 42mcg/spray (Vancenase Pockethaler) from the BCF at the May meeting. The committee modified the BCF listing to state that each facility must have at least one nasal corticosteroid on its formulary. The committee also indicated its intention to review the corticosteroid nasal inhalers at the next meeting to see if a specific inhaler should be selected for the BCF in order to standardize availability across the MHS.

   The committee reviewed information on corticosteroid inhalers presented by LCDR Richerson and unanimously decided to add fluticasone nasal spray (Flonase) to the BCF. The class remains open on the BCF. Based on current DAPA prices and the number of puffs per day required for maintenance therapy in adults, fluticasone is 20% less expensive than flunisolide (Nasalide) 25 mcg/spray (see Appendix C). Allergy/immunology specialists reviewed the dosing, which was based on package labeling for each product. The specialists expressed the opinion that fluticasone would be a good selection as a “workhorse” nasal corticosteroid on the BCF based on their clinical experience, the information in Appendix C, and the fact that fluticasone is approved for use in patients as young as 4 years old.

G. Agents considered for BCF and NMOP formulary status:

1. *Rofecoxib (Vioxx; Merck)*: The committee did not add rofecoxib to the BCF, but approved the addition of rofecoxib to the NMOP formulary subject to prior authorization. Although committee members expressed concern that Merck Medco's prior authorization criteria allow prescriptions to be filled for short-term use for pain, the committee elected to adopt the existing Merck Medco prior authorization criteria for rofecoxib because criteria customized for DoD could take at least 90 days to implement. The percentage of prescriptions for rofecoxib that will be written for short-term therapy is unknown. The same subcommittee that was tasked to quantify the value of the NMOP prior authorization program was also tasked to quantify the usage of rofecoxib for short-term therapy.

   Rofecoxib was approved by the FDA on 20 May 99 for the treatment of osteoarthritis (OA), acute pain, and primary dysmenorrhea. Like celecoxib (Celebrex; Searle/Pfizer) rofecoxib is an NSAID that is highly selective for cyclooxygenase-2 and is commonly known as a COX-2 inhibitor. Unlike celecoxib, rofecoxib is not indicated for rheumatoid arthritis, although trials are underway. Celecoxib currently lacks indications for acute pain and primary dysmenorrhea. The use of rofecoxib for pain for more than 5 days has not studied. Rofecoxib, unlike celecoxib, is not a sulfonamide and is not contraindicated for patients allergic to sulfa drugs. Like celecoxib, rofecoxib is significantly more costly than other NSAIDs. Rofecoxib appears to be no more effective than other NSAIDs, including celecoxib, in relieving pain and inflammation; the potential benefit of the COX-2 inhibitors is primarily related to a potential reduction in the incidence of GI adverse events. Data on actual outcomes is yet not available for either celecoxib or rofecoxib. There does not appear to be any advantage in using the selective COX-2 inhibitors short-term for pain as compared to other NSAIDs, given the extreme rarity of GI events after short-term therapy.

2. *Rosiglitazone (Avandia; SmithKline Beecham)*: The committee added rosiglitazone to the NMOP formulary and did not add it to the BCF. Rosiglitazone was approved by the FDA on 25 May 99 as an adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes mellitus, both as monotherapy and in combination with metformin (Glucophage; Bristol-Myers Squibb). Rosiglitazone has been studied in combination with sulfonylureas and insulin, although these combinations are not yet FDA approved. Rosiglitazone is a thiazolidinedione antidiabetic agent that acts primarily as an insulin sensitizer. There are currently three thiazolidinediones on the market: rosiglitazone, troglitazone (Rezulin; Parke-Davis), and pioglitazone (Actos; Takeda). Pioglitazone was approved by the FDA in mid-July and has not yet come up for P&T committee review.

   The primary difference between troglitazone and rosiglitazone appears to be the reported incidence of hepatotoxicity. LTC Rick Downs reported on the comparative safety, tolerability, effectiveness, and price of the two agents. The FDA recently withdrew the monotherapy indication for troglitazone and tightened requirements for monitoring liver enzymes in light of reports of 28 deaths and 40 liver transplants associated with a denominator of approximately a million patients exposed to the drug—an incidence of between 3-4 events per 100,000 patients. There have been no indications of

hepatotoxicity with rosiglitazone in clinical trials involving approximately 4000 patient-years of follow-up. However, according to the FDA, in order to have a 95% chance of discovering side effects that occur at an incidence of greater than 1 in 1000, a patient population of at least 3000-4000 patients is required. Because liver failure and death clearly occur much less frequently than 1 in 1000, there is insufficient evidence to draw firm conclusions about the risk of hepatotoxicity associated with rosiglitazone. There are some pharmacokinetic differences between the two drugs that are consistent with a hypothesis of less hepatoxicity with rosiglitazone than troglitazone.

Effectiveness may be considered to be a function of compliance and efficacy. Compliance with the two drugs is expected to be about the same, since both are dosed qd to bid. The actual reduction in HbA1C is modest, with 200 mg of troglitazone lowering HbA1c about as much as 2 mg bid of rosiglitazone and 400 mg of troglitazone about as efficacious as 4 mg bid of rosiglitazone. At this dose equivalence, rosiglitazone appears to cost somewhat more than troglitazone, since 4 mg once daily does not appear to work as well as 2 mg bid: $1.85 for 200 mg troglitazone *vs*. $2.l6 for 2 mg bid of rosiglitazone, and $2.94 for 400 mg of troglitazone 400 mg *vs*. $2.98 for 4 mg bid of rosiglitazone. LTC Downs proposed that rosiglitazone be retained in a pending category until the next meeting in order to more clearly define the risk of hepatotoxicity associated with the drug.

After extensive discussion, the committee concluded that there is no evidence that rosiglitazone offers a safety, efficacy, or cost advantage compared to other drugs on the market. However, leaving the drug in the "pending review" category on the NMOP formulary would likely just cause patients to obtain the drug through retail network pharmacies at a higher cost. The committee decided to add rosiglitazone to the NMOP formulary since delaying its availability through the NMOP is not likely to affect overall utilization of the drug. The committee will review this class of drugs again at the next meeting.

3. *Cilostazol (Pletal; Pharmacia & Upjohn)*: The committee added cilostazol to the NMOP formulary as a non-preferred drug, with pentoxifylline as the preferred alternative for this indication. Cilostazol was not added to the BCF.

   Cilostazol was approved by the FDA on 15 Jan 99 for the treatment of intermittent claudication, a condition that affects an estimated 18,000 to 30,000 patients in DoD. The only other drug that is currently indicated for intermittent claudication is pentoxifylline. Cilostazol is a PDE III inhibitor, a class of drugs that has been associated with increased mortality in cardiac patients. Cilostazol was approved by the FDA with a black box warning stating that it is not to be used in patients with CHF of any severity (about 10-15% of patients with intermittent claudication have CHF). In addition, the FDA was concerned about the lack of data on the use of cilostazol concurrently with clopidogrel (Plavix). Phase IV trials to more clearly define the safety of this drug are currently either in the planning stages or underway. Cilostazol costs approximately $1.78/day, compared to about $0.44/day for generic pentoxifylline, but may prove to be more efficacious.

After 24 weeks, cilostazol increased pain-free walking distances of intermittent claudication patients by about 107 meters (117 yards), compared to 65 meters (71 yards) with pentoxifylline.

The committee designated cilostazol as a non-preferred drug, with pentoxifylline as the preferred alternative on the NMOP formulary because of the safety issue as well as comparative costs. The committee will review any available information concerning safety, the volume of calls being made, and comparative costs at the next meeting.

4. *Zanamivir (Relenza; GlaxoWellcome)*: The committee excluded zanamivir from the NMOP formulary and it was not added to the BCF. Zanamivir was approved by the FDA 27 July 99. Zanamivir is an orally inhaled neuraminidase inhibitor given twice daily for 5 days for the treatment of uncomplicated acute illness due to influenza in adults and adolescents older than 12 years of age who have been symptomatic for no more than 2 days. It decreases flu symptoms and shortens the duration of symptoms by approximately 1 to 1.5 days. Although zanamivir was primarily tested in influenza A, it also appears to be active against influenza B. There is evidence that zanamivir is also effective in prevention. MAJ Barbara Roach (PEC) reported that use of the drug is likely to be limited in DoD due to the widespread administration of flu shots. In addition, other drugs with influenza A activity (e.g., amantadine, rimantadine) are available both as chemoprophylaxis and treatment, although they may cause CNS side effects. Zanamivir may cause bronchospasm in susceptible patients and has not been studied in children under 12 or in a large number of elderly patients with comorbid disease. The DAPA price for zanamivir is likely to be about $28.00 for a 5-day regimen, compared to approximately $1.20 - $13.60 for 10 days of treatment with amantadine or rimantadine, respectively. Use of zanamivir is likely to be most rational during outbreaks of the flu and then only for individuals who cannot tolerate the antiviral drugs. Another potential use may be during outbreaks of influenza B. The NMOP is not an appropriate source for zanamivir because the NMOP could not provide the medication quickly enough for it to be effective for patients.

H. At the May meeting a subcommittee was appointed to investigate the issue of fertility drugs in greater detail, obtain input from individuals outside of the P&T Committee if necessary, and recommend actions to make the coverage of fertility drugs consistent in the NMOP and the retail pharmacy networks. CDR Egland reported that the subcommittee has reviewed applicable law and federal regulations pertaining to fertility drugs and is working on a plan to make the coverage of fertility drugs consistent in the NMOP and the retail pharmacy networks. The plan will be brought back to the committee, which may then decide whether to submit the plan to TMA with its recommendations and/or requests for changes in current policy. The subcommittee will provide an interim report at the next meeting.

I. Although follitropin alfa (Gonal-F, Serono) and follitropin beta (Follistim, Organon) were not explicitly listed on the previous NMOP preferred drug list (PDL), prescriptions for both agents have been being filled through the NMOP on an ongoing basis. Because these agents were not on the PDL, they were not picked up for the Covered Injectables list during the

restructuring of the NMOP Formulary. Follitropin alfa and beta are fertility agents similar to others on the Covered Injectables list. Both can be given subcutaneously. The committee decided to add follitropin alfa (Gonal-F) and follitropin beta (Follistim) to the NMOP Covered Injectables List.

J. The committee discussed current policies regarding drug therapy for weight reduction, in light of the recent FDA approval of orlistat (Xenical), a non-systemic lipase inhibitor that reduces the absorption of dietary fat. After consideration of the policies governing dispensing of drugs through the NMOP, the committee agreed that orlistat could not be added to the NMOP Formulary since drug therapy for weight reduction is not a covered benefit. The committee also agreed that orlistat is not appropriate for the BCF.

   Further discussion centered on the necessity for alignment of policy with the current philosophy of prevention and the move from a fee-for-service system to managed healthcare. The committee agreed that it should formulate an opinion on the issue of weight reduction that could be passed along to other venues for consideration. The committee appointed a subcommittee to formulate a statement regarding weight reduction policy for the committee to consider at the next meeting. Subcommittee members include MAJ Barbara Roach, LTC Rick Downs, COL Humberg, CAPT Hostettler. COL Humberg will report recommendations and proposed policy changes (if appropriate) to TMA.

K. The committee discussed pending changes in the TRICARE/CHAMPUS Policy Manual that will apply quantity limits and prior authorization requirements to the retail network. The quantity limits and prior authorization requirements will be consistent with those in the NMOP
   .

L. The Quantity Limits Subcommittee [MAJ Bellemin, Danielle Doyle, Ray Nan Berry (Foundation Health), Eugene Moore (PEC)] submitted a proposed list of quantity limits to the committee. The quantity limits will also apply to the retail network pharmacies when changes to Chapter 7, Section 7.1 of the TRICARE/CHAMPUS policy manual are finalized. After considerable discussion and modification of some quantity limits, the committee approved the list of quantity limits shown in Appendix D. Specific matters of discussion for which reports are due to the committee are listed below:

   - *Zolpidem (Ambien)*—The committee approved the proposed limit of 10 tablets in 30 days for mail order proposed by the subcommittee, but requested that MAJ Bellemin report back to the committee at the next meeting concerning the number of prescriptions returned to the patient because of exceeding the maximum daily dose. This concern was based on literature support for use of zolpidem in psychiatric disorders more frequently than once per day. Tom Kellenberger from Merck-Medco explained that the usual procedure for prescriptions that exceed the maximum daily dose is to call the physician and obtain an affidavit that the physician understands the maximum and accepts responsibility. If the physician cannot be contacted, the prescription is returned to the patient.

- *Blood products/biotech products*— The committee discussed the difficulty of determining actual quantity limits for these medications, which tend to be very dependent on patient-specific factors. Quantity limits are easier to administer if they are expressed as the maximum amount of medication provided per copayment or period of time. However, it is difficult to decide where to set the maximum amount, since prescriptions may be written "as directed." Options discussed included increasing the current "30-days supply" limit to 45 days, increasing the limit to 90 days, or eliminating quantity limits for this category. The committee agreed that some control is desirable due to the high cost of these agents and the possibility that the patient might experience side effects necessitating discontinuation, might no longer require, or might not respond to the drug. The committee requested that Merck-Medco report back to the committee with the customary dose, supply, and refill quantity of blood products and biotech drugs being dispensed by Merck-Medco.
- *Topicals:* The committee was unable to reach consensus on the six topical agents selected for the quantity limits list. Merck-Medco was asked to report back to the committee with the customary dose, supply, and refill quantity of these agents in order to better quantify reasonable quantity limits. Bill Hudson (Humana) will also report on utilization through managed care.
- *Antibiotic quantity limits* – MAJ Bellemin will report at the next meeting concerning any issues with the current limits and report on utilization.
- *Injectable fertility agents:* The committee requested that MAJ Bellemin report back at the next meeting concerning utilization of injectable fertility agents to determine whether the current 20 amp per prescription limit is adequate (since the quantity may increase with each cycle). MAJ Bellemin will also report on current prior authorization policies and issues concerning fertility treatment.

The quantity limit for etanercept injection (Enbrel) was increased to a 6-week supply (3 cartons of 4 injections) in the NMOP. This will decrease the likelihood that patients would run out of medication between refills, and it increases the incentive for filling prescriptions for the drug through the NMOP as compared to the retail network pharmacies.

M. Anthem Alliance requested that the P&T Committee review a proposed utilization program for non-sedating antihistamines. The request was referred to the P&T committee by TMA-West in order to ensure proper coordination and support for the goal of having the MCSC, NMOP, and MTFs provide the same equitable, consistent, and cost-effective benefit. The request led to a general discussion about coordinating national contracting efforts, DAPA incentive agreements, DoD P&T formulary decisions, regional/MTF formulary decisions, and managed care contractor utilization programs. The committee did not endorse the Anthem Alliance proposal because:

- Utilization programs should ideally be applied consistently across the retail pharmacy networks for all TRICARE regions. A decision to apply should a program across all regions would require more in depth analysis and extensive coordination to obtain agreement by all MCSC.

- ♦ The PEC plans to review the non-sedating antihistamine drug class for the BCF and the NMOP formulary. The drug class may be appropriate for a contacting initiative or DAPA incentive agreement. Anthem Alliance may want to ensure that its utilization management program is in agreement with BCF and NMOP formulary decisions.

N. The Advances in Medical Practice (AMP) funding initiative will provide additional funding to the Defense Health Program in FY 00 and beyond. This funding initiative is designed to support the adoption of technological advances in medical care. The Surgeons General have identified funding for pharmacy—specifically new drug technologies—as one of the areas where this money could be utilized. The committee empowered a subcommittee to make recommendations and decisions concerning the use of these funds. Subcommittee members include: COL Rosa Stith, CDR Mark Brouker, LCDR Mark Richerson, CDR Terry Egland, MAJ Mickey Bellemin.

O. Pharmaceutical manufacturers typically distribute "starter packs" for free in the private sector. MTF pharmacies cannot accept free goods unless they comply with cumbersome regulations governing the acceptance of gifts by the government. CDR Egland suggested that MTFs could buy starter packs in bulk for a minimal fee in order to facilitate initial therapy. CAPT Hostettler agreed to address this issue with DSCP and will report back to the committee at the next meeting.

P. The committee discussed the procedure for interim committee decisions. CDR Egland stated that while ideally he would prefer to present proposals for discussion via electronic connections, sometimes the co-chairs will have to decide issues on an interim basis. The committee agreed that interim decisions should be communicated to the committee via e-mail. A standing report of all interim decisions will be placed as one of the first items on the agenda at each meeting.

7. ADJOURNMENT: The meeting adjourned at 1400 hours. The next meeting will be held on Thursday, November 18th at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas, beginning at 0800 hours. All agenda items are to be submitted to the DoD PEC no later than Friday, October 15th.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chairman	Co-chairman

Appendix A: Non-Preferred Drugs/Preferred Alternatives in the NMOP

Table 1. Annual cost avoidance to DoD and workload impact on Merck-Medco: Old PDL NMOP Formulary as compared to restructured NMOP Formulary

	Estimated Annual Cost Avoidance to DOD	Phone Calls Generated as a Percent of Total Rx's Filled†	Cost Avoidance Per Phone Call
Old NMOP Formulary	$171,000[1]	2.00%[2]	$7
Restructured NMOP Formulary	$587,713[3]	1.57%[4]	$30
Net Change	**$416,713**	**(0.43%) or 22% decrease**	**$23**

† Actual phone calls generated by Merck-Medco during report period divided by actual prescriptions filled by Merck-Medco during same report period.

1. The vast majority of 'mapped drugs' used previous to the May 1999 DoD P&T committee by Merck-Medco resulted in saving to DoD of less than $1,000/year. In fact, some of the mapping requests actually resulted in cost increases to DoD. Assuming that each of the estimated 342 previously mapped drugs saved DoD $500/year, we estimate that the cost savings from the previous list of mapped drugs was $171,000/year (342 x $500).
2. Phone calls generated by Merck-Medco during report period of 21 November 1998 through 27 March 1999 (8142) divided by actual prescriptions filled by Merck-Medco during same reporting period (406,040).
3. Estimated, based on switch rate data (29 May 1999 -31 July 1999), current DAPA prices and CY98 NMOP usage data.
4. Phone calls generated by Merck-Medco during report period of 29 May 1999 through 31 July 1999 (3720) divided by actual prescriptions filled by Merck-Medco during same reporting period (237,346).

Table 2. Phone calls generated for Merck-Medco and projected cost avoidance to DoD if Pepcid, Axid, Vasotec and nitroglycerin patches are included as non-preferred drugs on the NMOP Formulary

Non-Preferred Drug	Preferred Drug	Switch Rate	Annual Cost Avoidance to DoD†	Phone calls (per year) generated for Merck Medco††	Cost Avoidance Per Phone Call
Minitran Deponit Transderm Nitro Nitrodisc, NTG patch generics	Nitrodur	74%*	$20,647	334	$62
Pepcid	Generic ranitidine	50%**	$152,919	2015	$76
Axid	Generic ranitidine	50%**	$40,389	915	$44
Vasotec	Lisinopril (Zestril)	52%*	$183,075	3585	$51
Total			**$397,030**	**6849**	**$58**

† Estimated, based on CY1998 NMOP usage data, current DAPA prices and estimated/actual switch rates.

†† From Merck-Medco. Represents number of new prescriptions filled for the non-preferred drug(s) in CY98. Assumes phone calls are made only on new prescriptions.

* Based on switch rates for specific non-preferred/preferred drug pair as provided by Merck-Medco.

** Switch rate data not available - switch rate assumed to be 50%.

Table 3. Annual cost avoidance to DoD and workload impact on Merck-Medco: Old PDL NMOP Formulary as compared to restructured NMOP Formulary plus Axid, Pepcid, Vasotec and nitroglycerine patches added as non-preferred drugs to the NMOP Formulary.

	Estimated Annual Cost Avoidance to DoD	Phone Calls Generated as a Percent of Total Rx Filled†	Cost Avoidance per Phone Call
Old NMOP Formulary[1]	$171,000	2.00%	$7
Restructured NMOP Formulary[1]	$587,713	1.57%	$30
Restructured NMOP Formulary plus Axid, Pepcid, Vasotec and nitroglycerine patches added as non-preferred drugs to the NMOP Formulary	$984,743[2]	1.88%[3]	$38
Net Change (Old NMOP Formulary as compared to proposed changes)	**$813,743**	**(0.12%) or 6% decrease**	**$31**

1. From Table 1.
2. Totals from Tables 1 and 2.
3. Estimated number of phone calls generated by Merck-Medco in the next 12 months (26,193) divided by projected number of prescriptions filled by Merck-Medco in the next 12 months [total prescriptions filled in May 1999, June 1999, July 1999 = 347,960 multiplied by 4 = 1,391,840]

Appendix B: Contract Implementation Results for Diltiazem (Tiazac)

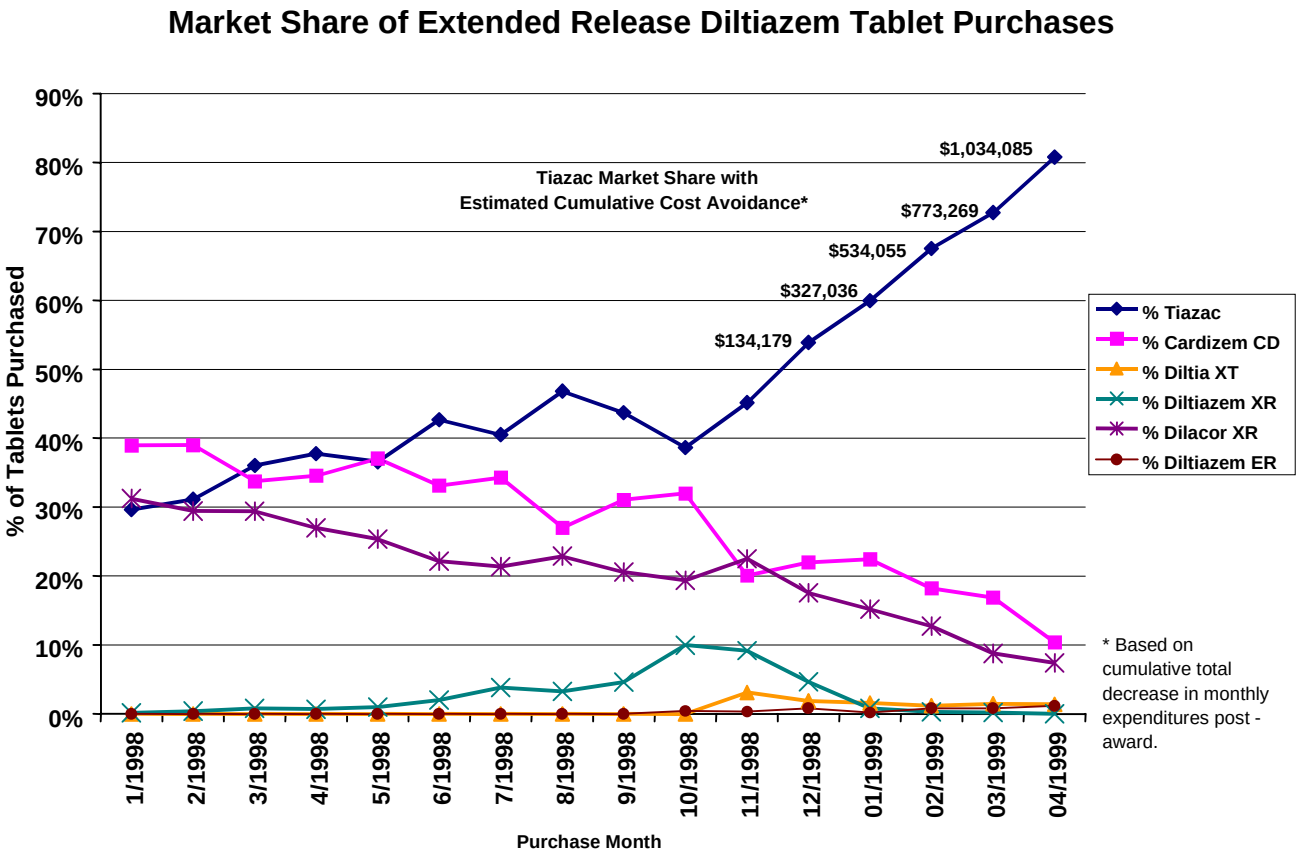

Figure 1: Market Share of Extended Release Diltiazem Tablet Purchases

Table 1: Impact of Diltiazem (Tiazac) Contract Over Time

(Contract Start Date: 12/15/98)

Month	Total Purchased	Total Cost	Cost per Tablet	Cumulative Cost Avoidance*
Jan 98	1,416,730	$919,553	0.649	0
Feb 98	1,261,430	$817,966	0.649	0
Mar 98	1,429,710	$911,019	0.634	0
Apr 98	1,568,720	$994,208	0.639	0
May 98	1,345,110	$860,270	0.628	0
Jun 98	1,401,220	$880,033	0.629	0
Jul 98	1,452,630	$913,433	0.601	0
Aug 98	1,383,700	$831,405	0.625	0
Sep 98	1,801,750	$1,125,832	0.582	0
Oct 98	1,472,300	$856,906	0.582	0
Nov 98	1,255,470	$655,365	0.522	0
Dec 98	1,481,370	$801,344	0.547	$134,179
Jan 99	1,461,310	$732,871	0.501	$327,036
Feb 99	1,404,200	$639,490	0.455	$534,055
Mar 99	1,510,620	$676,970	0.448	$773,269
Apr 99	1,482,210	$593,330	0.40	$1,034,085

* Where applicable, cumulative cost avoidance calculated as follows:

a. Total units purchased for each drug and strength were multiplied times the prices in effect prior to the contract award.

b. Total units purchased for each drug and strength were multiplied times the prices in effect after the contract award.

c. Results of b. above were subtracted from a. above.

Appendix C: Nasal Corticosteroid Cost Analysis

Trade Name	Generic Name	Manufacturer	Sprays Per Unit	Average Price Paid Calendar Year 1998	Current Unit Cost (based on DAPA prices as of 1 Aug 99)	Change in Unit Cost	Dosing Frequency	Maintenance Puffs per Day (Adult)	Maintenance Cost / Month	Age range
Flonase	fluticasone 50mcg/spray	Glaxo	120	$10.68	$11.12	4%	QD	2	$5.56	4 to adult
Nasalide	flunisolide 25 mcg/spray	Dura	200	$11.24	$11.65	4%	BID	4	$6.99	6 to adult
Vancenase Pockethaler*	beclomethasone 42mcg/spray	Schering	200	$3.76	$9.25	146%	TID	6	$8.33	6 to adult
Vancenase AQ DS	beclomethasone 84mcg/spray	Schering	120	$10.75	$18.96	76%	QD	2	$9.48	6 to adult
Nasacort AQ	triamcinolone 55mcg/spray	RPR	120	$7.74	$18.96	145%	QD	2	$9.48	6 to adult
Nasonex	mometasone 50 mcg/spray	Schering	120	$8.87	$10.49	18%	QD	4	$10.49	12 to adult
Nasacort*	triamcinolone 55mcg/spray	RPR	100	$8.28	$18.22	120%	QD	2	$10.93	6 to adult
Nasarel	flunisolide 25 mcg/spray	Dura	200	$7.18	$18.73	161%	BID	4	$11.24	6 to adult
Rhinocort*	budesonide 32mcg/spray	Astra	200	$12.46	$19.00	52%	BID	4	$11.40	6 to adult
Vancenase AQ	beclomethasone 42mcg/spray	Schering	200	$9.07	$19.50	115%	BID	4	$11.70	6 to adult
Beconase AQ	beclomethasone 42mcg/spray	Glaxo	200	$18.53	$20.96	13%	BID	4	$12.58	6 to adult
Beconase*	beclomethasone 42mcg/spray	Glaxo	200	$12.36	$14.68	19%	TID	6	$13.21	6 to adult
Beconase*	beclomethasone 42mcg/spray	Glaxo	80	$5.85	$8.21	40%	TID	6	$18.47	6 to adult
Vancenase*	beclomethasone 42mcg/spray	Schering	80	$15.89	$14.06	-12%	TID	6	$31.64	6 to adult

*** Metered Dose Inhaler**

Appendix D: Quantity Limits for NMOP and Retail Pharmacy Network

The quantity of medication dispensed is generally limited to a 90-day supply in the National Mail Order Pharmacy (NMOP) and a 30-day supply in retail network pharmacies. If a patient obtains more than a 30-day supply at a retail pharmacy, the patient must pay an additional co-pay for each additional 30-day supply increment, up to a 90-day supply (3 co-pays).

A subcommittee of the DoD P & T Committee and Pharmacoeconomic Center (PEC) staff members developed proposed quantity limits that either (1) deviate from the general 30- or 90-day limits, or (2) specify the quantity that is associated with a specific time period. The following table shows the proposed quantity limits and the rationale for these limits. If a specific rationale is not stated, the quantity limit was calculated by multiplying the maximum daily dose times the days supply limit.

A quantity limit represents the maximum allowable quantity that may be dispensed for a given time period. Maximum quantities to be dispensed are determined by directions for use or the proposed quantity limits below, whichever is less.

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Antiemetics			
Granisetron 1mg tablet (Kytril)	None	Retail: 8 per 30 days Mail: 24 per 90 days	Indication is for 1 tablet (1 mg) twice daily on days that chemotherapy is given. Most chemotherapy regimes are for 4 or 5 days per cycle. However, Drug Facts & Comparisons lists several chemo regimens (e.g., COPP for lymphoma) that require oral therapy with highly emetogenic drugs for periods ranging from 8 to 14 days per cycle.
Ondansetron 4mg and 8mg (Zofran)	45 tablets or 90 days, whichever is less	Retail: 15 per 30 days Mail: 45 per 90 days	Indication is for 1 tablet (4 or 8 mg) twice daily on days that chemotherapy is given, and for 1 or two days after regimen is finished. Most chemotherapy regimes are for 4 or 5 days per cycle. However, Drug Facts & Comparisons lists several chemo regimens (e.g., COPP for lymphoma) that require oral therapy with highly emetogenic drugs for periods ranging from 8 to 14 days per cycle.
Dolasetron 50mg and 100 mg (Anzemet)	None	Retail: 5 per 30 days Mail: 15 per 90 days	Indication is for 1 tablet (50 or 100 mg) prior to chemotherapy. Most chemotherapy regimes are for 4 or 5 days per cycle. However, Drug Facts & Comparisons lists several chemo regimens (e.g., COPP for lymphoma) that require oral therapy with highly emetogenic drugs for periods ranging from 8 to 14 days per cycle.
Oral and Nasal Inhalers			
Albuterol Inh Soln 20ml (0.5%)	9 units (180ml) or 90 days, whichever is less	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Albuterol Inhaler	5 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Beclomethasone AQ Nasal Spray 19gm (Beconase)	3 units or 90 days, whichever is less	Retail: 1 units per 30 days Mail: 3 units per 90 days	
Beclomethasone Inhaler 16.8 gm	9 units or 90 days, whichever is less	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Beclomethasone Nasal Inhaler (Beconase, Vancenase)	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Bitolterol Inhaler 15cc (Tornalate)	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Budesonide (Pulmicort)	None	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Budesonide Nasal Inhaler 7gm (Rhinocort)	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Cromolyn Sodium Inhaler 112 Puff (Intal)	6 units or 90 days, whichever is less	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Cromolyn Sodium Inhaler 200 Puff (Intal)	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Cromolyn Sodium Nebulizing Soln (20mg)	360 units or days, whichever is less	Retail: 150 units per 30 days Mail: 450 units per 90 days	
Flunisolide Inhaler (Aerobid, Aerobid-M)	7 units or 90 days, whichever is less	Retail: 3 per 30 days Mail: 9 per 90 days	
Flunisolide Nasal Soln (.025%)	7 units or 90 days, whichever is less	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Fluticasone 110mcg (Flovent)	6 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Fluticasone 220mcg (Flovent)	6 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Fluticasone 44mcg (Flovent)	None	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Fluticasone Nasal Spray (Flonase)	3 units or 90 days, whichever is less	Retail: 1 units per 30 days Mail: 3 units per 90 days	
Ipratropium 0.03% Nasal Spray 30ml (Atrovent)	3 units or 90 days, whichever is less	Retail: 1 unit per 30 days Mail: 3units per 90 days	
Ipratropium 0.06% Nasal Spray 15ml	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	Indicated for rhinorrhea associated with the common cold. 16 Sprays per day maximum. 165 sprays per container. Appropriate, because a common cold is a self-limiting illness.
Ipratropium Inhalant Soln 2.5ml (.02%)	360 units or 90 days, whichever is less	Retail: 150 units per 30 days Mail: 450 units per 90 days	
Ipratropium Inhaler	6 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Metaproterenol Inhalant Soln (0.6%)	None	Retail: 150 units per 30 days Mail: 450 units per 90 days	
Metaproterenol Inhaler (Alupent)	6 units or 90 days, whichever is less	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Triamcinolone Aqueous Nasal Spray (16.5gm) (Nasacort)	6 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Nedocromil Inhaler (Tilade)	6 units	Retail: 3 units per 30 days Mail: 9 units per 90 days	
Pirebutolol Inhaler 300 puff (Maxair) Inh	4 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Pirebutolol Autohaler 400 inh	3 units or 90 days, whichever is less	Retail: 1 unit per 30 days Mail: 3 units per 90 days	

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Salmeterol (Serevent)	6 inhalers or 90 days, whichever is less	Retail: 1 inh per 30 days Mail: 3 inh per 90 days	
Triamcinolone oral Inhaler (Azmacort)	6 units or 90 days, whichever is less	Retail: 2 units per 30 days Mail: 6 units per 90 days	
Antimigraine Drugs			
Note on dosing of 5HT-1 receptor antagonists for treatment of migraine. Generally for an acute migraine attack, the 5HT-1 antagonists are given once, and the dose is repeated in 4 hours if the headache returns or is still present. This is expected to successfully abort a classical migraine attack in 68% to 86% of patients. Subsequent doses may be given at 4-hour intervals, up to the maximum amount specified in a 24-hour period. Safety of treating more than 4 headaches in a 30-day period has not been established. [2,3,4]			
Dihydroergotamine Nasal Spray (Migranal)	None	Retail: 8 units per 30 days Mail: 24units per 90 days	Safety of using more than 3mg/24 hour or 4mg in a 7-day period has not been established.[2,3,4]
Naratriptan 1mg (Amerge)	8 tablets or 30 days, whichever is less	Retail: 9 tabs per 30 days Mail: 27 tabs per 90days	Two tablets per headache, 4 headaches per month. If more than 8 tablets are required, patient should be receiving 2.5 mg tablets.[2,3,4] (Tablets packaged in 9's)
Naratriptan 2.5mg Tablet (Amerge)	8 tablets or 30 days, whichever is less	Retail: 9 tabs per 30 days Mail: 27 tabs per 90 days	Two tablets per headache, 4 headaches per month. Max of 5mg in 24 hours.[2,3,4] (Tablets packaged in 9's)
Rizatriptan 5mg, 10mg Tablet, MLT-5mg, 10mg Tablet 16.8 gm (Maxalt)	None	Retail: 12 tabs or 30 days Mail: 36 tabs or 90 days	Two tablets per headache, 4 headaches per month. Max of 30mg in 24 hours. If more than 12 of the 5mg tablets are needed, patient should be changed to 10mg tablets.[2,3,4]
Sumatriptan 25mg Tablet (Imitrex)	48 tablets or 30 days, whichever is less	Retail: 18 tabs or 30 days Mail: 54 tabs or 90 days	Max of 200 mg (8 tablets) in 24 hours, 4 headaches per month. If more than 18 25-mg tablets are needed in 30 days, patient should move to the 50-mg tablet.[2,3,4] (AWP is the same for both strengths)
Sumatriptan 50mg Tablet (Imitrex)	48 tablets or 30 days, whichever is less	Retail: 18 tabs or 30 days Mail: 54 tabs or 90 days	Max of 200mg (4 tablets) in 24 hours, 4 headaches per month.[2,3,4]
Sumatriptan Injection (Imitrex)	8 injections (4ml) or 30 days, whichever is less	Retail: 8 units per 30 days Mail: 24 units per 90 days	2 injections per 24 hours, maximum recommended. 4 headaches per month.
Sumatriptan Nasal Spray 5mg/unit, 20mg/unit (Imitrex)	None	Retail: 6 units per 30 days Mail: 18 units per 90 days	Packaged in 6's. Maximum of 40 mg/24 hours. If more than 6 units of 5 mg required, should consider 20 mg.[2,3,4]
Zolmitripan 2.5mg and 5mg Tablet (Zomig)	None	Retail: 8 tabs or 30 days Mail: 24 tabs or 90 days	Two tablets per headache, 4 headaches per month. If more than 8 of the 2.5mg tablets are needed, patient should be changed to 5mg tablets.[2,3,4]
Miscellaneous			
Alcohol Swabs	1 swab per syringe	1 swab per syringe rounded up to nearest 100	
Blood/Urine Test Strips	90 days supply or 400 units, whichever is less	90 days supply or 400 units, whichever is less	
Butorphanol NS (Stadol)	4 units or 30 days, whichever is less	Retail: 4 units per 30 days Mail: 4 units per 30 days	Indicated for acute, severe pain. Maximum 4 mg (sprays)/day. 14 sprays/unit.

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Dornase Alpha (Pulmozyme)	60 ampules or 30 days, whichever is less	Retail: 30-day supply or 120 amps, whichever is less Mail: 90-day supply or 360 amps, whichever is less	Recommended daily dose is 1 amp per day, some patients may benefit from 1 amp BID. However, some patients receive 4 amps BID, two weeks on - two weeks off.[6]
Etanercept injection (Enbrel)	None	Retail: 8 injections (2 cartons of 4 injections) (4 weeks supply) Mail: 12 injections (3 cartons of 4 injections) (6 weeks supply)	Indicated use is for one injection twice weekly. Patients must meet prior authorization criteria for etanercept.
Insulin Syringes & Needles	90 days supply or 400 units, whichever is less	90 days supply or 400 units, whichever is less	
Ketorolac 10mg Tablet (Toradol)	None	Retail: 20 tabs per 5 days Mail: 20 tabs per 5 days	Safety.[3] There were deaths from renal toxicity associated with this drug. Boxed warning is for acute treatment of pain, 4 tablets per day, for 5 days maximum per treatment episode.
Schedule III, IV, V Drugs for non-active duty only	Up to a max of 30 day supply and 5 refills	Retail: max of 30-day supply and 5 refills Mail: max of 30-day supply and 5 refills	Federal and State laws
Phenobarbital, Pemoline, other ADHD drugs	Up to a max of a 90 day supply and 1 refill	Retail: max of 90-day supply and 1 refill Mail: max of 90-day supply and 1 refill	Exception to above laws when used for seizure disorder and ADHD
Tramadol 50 mg (Ultram)	None	Retail: 240 tabs per 30 days Mail: 720 tabs per 90 days	FDB limit[7] There was toxicity and deaths associated with this drug. Boxed warning is for no more than 8 tablets per day.
Zolpidem 10mg Tablet (Ambien)	None	Retail: 10 tabs per 30 days Mail: 10 tabs per 30 days	
Antifungals			
Fluconazole 150mg (Diflucan)	1 tablet/90 days	Retail: 1 tablet per 30 days Mail: 3 tablets per 90 days	One tablet a month of the 150 mg strength is indicated for prophylaxis in 5% of patients.[8]
Oral Antifungals	None	Retail: 30 days supply maximum Mail 90 days supply maximum	While medically indicated for onychomycosis, lifestyle changes are also important.
Terconazole Vaginal Cream (Terazol-3)	1 box (20gm) or 30 days	Retail: 1 box (20 gm) per 30 days Mail: 1 box (20 gm) per 30 days	Short term med
Terconazole Vaginal Cream (Terazole-7)	1 box (45gm) or 30 days	Retail: 1 box (45gm) per 30 days Mail: 1 box (45gm) per 30 days	Short term med
Terconazole Vaginal Suppositories (Terazole-3)	1 box (3 units) or 30 days	Retail: 1 box (3 units) per 30 days Mail: 1 box (3 units) per 30 days	Short term med

Drug	Previous NMOP Limit	New Quantity Limits	Rationale
Ophthalmics			
Antibiotic Ophthalmics	None	Retail: 1 unit per 15 days Mail: 1 unit per 15 days	Short term med, not appropriate for mail order
Antiviral Ophthalmics	None	Retail: 1 unit per 15 days Mail: 1 unit per 15 days	Short term med, not appropriate for mail order
Ketorolac Opth (Acular) 3,5,10ml	None	Retail: 2 units per 30 days Mail: 6 units per 90 days	Two units of the 10ml would accommodate the maintenance dose. Smaller package sizes are appropriate for short-term indications.
Latanoprost (Xalatan) 2.5 ml	None	Retail: 2 units/30 days Mail: 6 units/90 days	Usual in most plans
NSAID ophthalmics Ocufen, Profenal, Voltaren	None	Retail: 1 unit per 15 days Mail: 1 unit per 15 days	Short term med, not appropriate for mail order
Olopatadine Hcl (Patanol) 5 ml	None	Retail: 2 units per month Mail: 2 unit per month	Usual in most plans.
Antibiotics			
Zithromax 250mg	6 tablets or 90 days, whichever is less	Retail: 6 tabs per 30 days Mail: 6 tabs per 30 days	Antibiotic, inappropriate for mail order
Zithromax 600mg	6 tablets or 90 days, whichever is less	Retail: 8 tabs per 30 days Mail: 24 tabs per 90 days	Prophylaxis of MAC at a dose of 2 tablets/week in HIV infected individuals
Fertility and Impotence			
Oral Fertility Agents (except clomiphene)	30 day supply	Retail: 30 day supply Mail: 30 day supply	
Injectable Fertility Agents	20 units or 30 days, whichever is less -no refills allowed.	Retail: 20 units per 30 days - no refills allowed Mail: 20 units per 30 days -no refills allowed	
Clomiphene citrate (e.g., Clomid)	10 tablets or 30 days, whichever is less	Retail: 10 tablets per 30 days Mail: 10 tablets per 30 days	
Alprostadil injection (Caverject, Edex)	6 injections or 30 days, whichever is less	Retail: 6 injections per 30 days Mail: 18 injections per 90 days	Health Affairs policy
Alprostadil intraurethral pellet (Muse)	6 pellets or 30 days, whichever is less	Retail: 6 pellets per 30 days Mail: 18 pellets per 90 days	Health Affairs policy
Sildenafil (Viagra)	6 tablets or 30 days, whichever is less	Retail: 6 tablets per 30 days Mail: 18 tablets per 90 days	Health Affairs policy

Notes/References:

1. Current TRICARE policy allows for patients to receive up to a 90-day supply at retail for most medications. Patients pay a co-payment for each month received.
2. Prescribing information. *Physician's Desk Reference, 52nd ed,* Medical Economics, Inc., Montvale, NJ, 1998.
3. *Drug Facts & Comparisons*, Facts & Comparisons, St. Louis, MO, 1999.
4. The average duration of headaches is 1-2 days, according to *Harrison's Principles of Internal Medicine*, 12ed., pp. 110-4. The typical migraine patient will experience an average of 3 attacks per month.[6] A range of 18 to 24 of the 50mg tablets monthly should be sufficient.
5. Hu XH, Markson LE, *et al.* Burden of Migraine in the United States: Disability and Economic Costs. *Arch Internal Med.* 1999;159(8):813-8.
6. Recommended daily dose, however, some patients receive 4 amps BID, two weeks on - two weeks off.
7. Safety information. First Data Bank, Indianapolis, IN, 1999.
8. *AHFS© Drug Information 1998.* American Society of Health System Pharmacists. Bethesda MD

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MCCS-GPE 17 May 1999

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 14 May 1999, at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, TX.

2. MEMBERS PRESENT:

COL Daniel D. Remund, MS	Co-chairman
CDR Terrance Egland, MC	Co-chairman
COL Rosa Stith, MC	Army
LTC Judith O'Connor, MC	Army
Danielle Doyle	Army
CDR Matt Nutaitis, MC	Navy
LCDR Denise Graham, MSC	Navy
LtCol John R. Downs, MC	Air Force
LtCol William Sykora, MC	Air Force
MAJ George Jones, BSC	Air Force
CDR Robert W. Rist	Coast Guard
LTC (P) George Crawford, MS	Joint Readiness Clinical Advisory Board
MAJ Steven Humburg, MC	Health Affairs
MAJ Mickey Bellemin BSC	Defense Supply Center Philadelphia (DSCP)
Ronald L. Mosier	Department of Veterans Affairs (alternate)
Ray Nan Berry	Foundation Health
William Hudson	Humana, Inc
Ron McDonald	Sierra Military Health Service
Gene Lakey	TriWest

3. OTHERS PRESENT:

CAPT Charlie Hostettler, MSC	DoD Pharmacy Program Director, TMA
CDR Mark Brouker, MSC	DoD Pharmacoeconomic Center
Lt Col Gary Blamire, BSC	Tricare Southwest Lead Agent
Lt Col (sel) Greg Russie, BSC	Air Force (alternate representative)
Tom Kellenberger	Merck-Medco Representative
Shelby Tanner, Jr.	Staff Judge Advocate, Fort Sam Houston
Shana Trice	DoD Pharmacoeconomic Center

4. ADMINISTRATIVE ISSUES:

   A. The minutes from the 5 February 1999 meeting were accepted as written.

   B. Committee membership: MAJ George Jones replaced Lt Col (sel) Greg Russie as the Air Force pharmacist committee member. Lt Col (sel) Russie will serve as the alternate Air Force pharmacist committee member. LCDR Denise Graham will enter a Duty Under Instruction (DUINS) Program. A Navy pharmacist has not yet been named to replace LCDR Graham on the committee. LTC Joel Schmidt, Walter Reed Army Medical Center, is the alternate Army physician member. LTC Kent Maneval, Walter Reed Army Medical Center, is the alternate Army pharmacist committee member.

5. OLD BUSINESS: Issues pending from previous meetings were addressed under new business because the committee needed to address the proposal to restructure the National Mail Order Pharmacy (NMOP) formulary as its first item of business.

6. NEW BUSINESS: Proposal to restructure the NMOP formulary.

   A. The committee approved a PEC proposal to replace the NMOP Preferred Drug List (PDL) with a restructured NMOP formulary. The restructured NMOP formulary is designed to:

      - Enable patients and providers to more easily and accurately determine the availability of medications in the NMOP.
      - Increase the use of medications that offer significant clinical or economic advantages compared to other medications.
      - Support compliance with DoD and joint VA/DoD pharmaceutical contracts.

   B. The NMOP Preferred Drug List (PDL) will be replaced by an NMOP formulary that includes specific injectable drugs and all non-injectable prescription drugs with the following exceptions or limitations:

- *Excluded drugs and drug classes:* Some drugs or classes of drugs are excluded from the NMOP formulary due to TRICARE policy or DoD P&T Committee decisions. These drugs are not available through the NMOP.
- *Drugs subject to prescribing guidelines or prior authorization:* These drugs must be dispensed in accordance with prescribing guidelines or prior authorization criteria that are established by the DoD P&T Committee.
- *Non-preferred drugs and preferred alternatives:* If the prescriber agrees that a preferred drug is clinically appropriate, a prescription for a non-preferred drug will be changed to a preferred alternative drug.
- *Covered injectable drugs:* The formulary includes selected injectable drugs that are intended for self-administration or are commonly administered in the home setting
- *Covered over-the-counter (OTC) drugs/products*: The formulary includes selected OTC drugs and products.
- *Drugs pending P&T committee review:* Drugs newly approved by the Food & Drug Administration (FDA) that are pending P&T Committee review will not be available through the NMOP until the P&T Committee completes the review and assigns the drug to the appropriate category on the NMOP formulary.

C. Appendix A identifies the drugs that are included in each formulary category in the initial edition of the NMOP formulary.

7. NEW BUSINESS: Agents considered for Basic Core Formulary and NMOP formulary status.

A. Celecoxib (Celebrex), commonly known as a COX-2 inhibitor, is indicated for relief of the symptoms of osteoarthritis and adult rheumatoid arthritis. A summary of efficacy, safety, and cost issues associated with celecoxib is provided at Appendix B. Committee decision: **Do not add to the BCF. Add to the NMOP formulary subject to a prescribing guideline/prior authorization.** Celecoxib is significantly more expensive than other non-steroidal anti-inflammatory drugs, so the prescribing guideline will be designed to target the use of celecoxib to patients who are at high risk for adverse gastrointestinal events. The committee discussed a draft prescribing guideline and provided precepts for the PEC to finalize the guideline. Celecoxib will be available through the NMOP when DSCP and Merck Medco have established procedures for implementing the prescribing guideline.

B. Brand name NSAIDS are 2 to 20 times more expensive than generic NSAIDs based on current DAPA prices. Generic NSAIDs, rather than brand name NSAIDs, should be used to the maximum extent consistent with patients' clinical needs. Committee decision: **The brand name NSAIDs listed below are designated as non-preferred drugs. The preferred alternatives are listed in Appendix 1.**

- nabumetone (Relafen)
- oxaprozin (Daypro)

- etodolac extended release (Lodine XL)
- diclofenac extended release (Voltaren XR)
- naproxen sodium extended release (Napralen)

C. Etanercept (Enbrel) is a new biotech inhibitor of tumor necrosis factor for use in patients with moderate to severe rheumatoid arthritis who have failed other agents. Discussion of a draft prescribing guideline centered on the number and identity of disease-modifying anti-rheumatoid drugs (DMARDS) that a patient must fail before receiving etanercept. The committee was also concerned that the prescribing guideline should take into account an apparent increased risk of serious infections that was recently detected through post-marketing surveillance of patients taking etanercept. The increased risk of serious infections prompted the FDA to revise the warnings section of the package insert for etanercept. The DAPA price for etanercept if $81.93 per dose, which equates to $655.44 per month of therapy. Committee decision: **Do not add to the BCF. Add to the NMOP formulary subject to prescribing guideline/prior authorization.** The committee provided precepts for the PEC to finalize the prescribing guideline. Etanercept will be available through the NMOP when DSCP and Merck Medco have established procedures for implementing the prescribing guideline. To limit the financial waste that occurs when patients discontinue the medication, the NMOP will dispense no more than a 30-day supply of etanercept (2 cartons of 4 injections).

D. Sevelamer hydrochloride (Renagel) is indicated for the reduction of serum phosphorus in patients with end-stage renal disease. It is a nonabsorbable hydrogel polymer that avoids the problems that are associated with phosphate binders containing aluminum or calcium. Aluminum-containing phosphate binders may cause aluminum toxicity resulting in osteomalacia, anemia, and dementia. Systemic absorption of calcium-containing phosphate binders may cause hypercalcemia and increased risk of metastatic calcification. Committee decision: **Do not add to BCF. Add to the NMOP formulary.**

E. Modafinil (Provigil) is used to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. In clinical trials modafinil showed significant improvement on objective and subjective measures of excessive daytime sleepiness compared to placebo. Direct comparisons of the efficacy of modafinil to other agents are not available. The National Transportation Safety Board has requested that the manufacturer conduct trials using modafinil in long-haul truckers to promote wakefulness. The committee expressed concern about the potential for inappropriate use of modafinil to increase alertness among patients who do not have narcolepsy. Committee decision: **Do not add to BCF. Add to the NMOP formulary and monitor usage patterns for evidence of inappropriate use.** (Note: the manufacturer estimates that only about 125,000 people suffer from narcolepsy in the United States, so usage of this drug should be minimal.)

F. Polyethylene glycol (Miralax) is an osmotic agent that is used as a laxative. Committee decision: **Do not add to the BCF. Add to the NMOP formulary.**

G. Corticosteroid oral inhalers: At the Feb 99 meeting the committee tabled action on a proposal to remove triamcinolone (Azmacort) inhaler from the BCF due to an announced DAPA price increase from $7.95 to $12.90 per inhaler. The DAPA price for Azmacort was subsequently reduced to $9.60 per inhaler. The DAPA price for beclomethasone (Vanceril) inhaler was recently increased from $3.45 to $5.75 per inhaler and Vanceril-DS inhaler went from $5.16 to $6.90 per inhaler. The cost per day for Vanceril, Vanceril-DS, and Azmacort inhalers is still less than the cost per day for other corticosteroids for oral inhalation. Committee decision: **Do not change the corticosteroid oral inhalers on the BCF, but continue to monitor price changes in this drug class. Vanceril, Vanceril-DS, and Azmacort remain on the BCF.**

H. Corticosteroid nasal inhalers: Beclomethasone 42mcg/spray (Vancenase Pockethaler) has been the only corticosteroid nasal inhaler on the BCF. The DAPA price for the Vancenase Pockethaler recently increased from $3.76 to $9.25 per inhaler. A PEC estimate of the monthly maintenance costs for various corticosteroid nasal inhalers (based on the dosing frequency and the number of sprays/puffs available in each on the inhalers) showed that the Vancenase Pockethaler no longer offers an economic advantage compared to other inhalers. Committee decision: **Remove beclomethasone 42mcg/spray (Vancenase Pockethaler) from the BCF. The BCF will state that the MTF must have a corticosteroid nasal inhaler on its formulary, but the MTF can select which one to have on its formulary.** The committee intends to review the corticosteroid nasal inhalers at the next meeting to see if a specific inhaler should be selected for the BCF in order to standardize availability across the Military Health System. (OPEN)

I. Premarin vs Ogen vaginal cream: Conjugated estrogen (Premarin) vaginal cream is currently on the BCF. An MTF requested a BCF modification that would allow the MTF to preferentially use estropipate (Ogen) vaginal cream instead of Premarin. There are no apparent differences in efficacy or safety between Premarin and Ogen vaginal creams. The DAPA price for Premarin vaginal cream is almost twice that of Ogen vaginal cream. Committee decision: **Change the BCF listing from conjugated estrogen vaginal cream to "estrogenic vaginal cream." All MTFs must include an estrogenic vaginal cream on their formularies, but the MTFs will select the specific brand.**

8. NEW BUSINESS: Other issues:

A. Fertility drugs: The TRICARE policy manual classifies noncoital reproductive technologies (artificial insemination, in vitro fertilization, gamete intrafallopian transfer, etc.) as noncovered treatments and specifies that services and supplies directly related to a noncovered procedure are not covered. Based on this policy, managed care support contractors in some TRICARE regions use prior authorization procedures to deny coverage at retail network pharmacies for fertility drugs when they are prescribed for use with noncoital reproductive technologies. Currently, the NMOP does not perform prior authorization procedures for fertility drugs. In some cases, the NMOP dispenses fertility drugs to patients who were previously denied coverage through a retail network pharmacy because the drugs were prescribed for use with noncoital reproductive technologies. The

committee concluded that this issue was too complex to be solved at the meeting. A subcommittee was appointed to investigate this issue in greater detail, obtain input from individuals outside of the P&T Committee if necessary, and recommend actions to make the coverage of fertility drugs consistent in the NMOP and the retail pharmacy networks. (OPEN)

B. Sildenafil (Viagra): The prescribing guideline that the PEC prepared for Merck Medco to fax to prescribers is still not used. The committee discussed the stipulation in the prescribing guideline that sildenafil will only be used for organic erectile dysfunction and hypothesized that provisions in the TRICARE policy manual are the basis for this stipulation. The committee reaffirmed that sildenafil should only be dispensed by the NMOP in accordance with the prescribing guideline.

C. Migraine drug usage in the NMOP: MAJ Bellemin reported that the NMOP receives very few complaints regarding the quantity limits for migraine drug therapy. Several committee members commented that the NMOP quantity limits are quite generous compared to quantity limits at MTFs or in other managed care settings. A subcommittee was appointed to review quantity limits for migraine drugs and submit recommendations to the P&T committee at the next meeting. (OPEN)

D. Niacin for antilipemic therapy: The committee reaffirmed its position that the NMOP should provide niacin (in both OTC and prescription forms) for antilipemic therapy. The committee does not intend that niacin should be provided for vitamin supplementation. A basis for the provision of OTC form of niacin may exist in the TRICARE final rule that established requirements and procedures for implementation of the TRICARE program. The TRICARE final rule allows the establishment of "other procedures for the effective operation of the pharmacy programs" to include drug formularies. While drug formularies are often viewed as a means to limit the availability of medications, the NMOP formulary could also be used to expand the availability of medications to include OTC forms of niacin for antilipemic therapy. The restructured NMOP formulary automatically includes prescription forms of niacin. Committee decision: **Add over-the-counter (OTC) forms of niacin prescribed for antilipemic therapy to the list of OTC items that are covered by the NMOP. Implementation is contingent on TMA West policy review.**

E. The discussion of OTC niacin led to a suggestion that needles, syringes, alcohol pads, and lancet should also be provided through the NMOP. Some committee members expressed concern that when co-pays and dispensing fees are taken into account, the beneficiaries would obtain very little benefit and the government would incur a substantial increase in cost. Other members suggested that costs to the government or the managed care support contractor are much higher if the beneficiary obtains such supplies through home health providers. Committee decision: **The NMOP should supply needles, syringes, and alcohol pads when a medication is dispensed for home injection. The NMOP should also supply alcohol pads and lancets for diabetic patients.** The provision of these items through the NMOP is contingent upon the ability of the NMOP COTR and

contracting officer identify methods by which these items can be provided at a reasonable cost.

F. Handling of high dollar items in the NMOP: The committee tabled this issue at the last meeting and asked the NMOP COTR, the PEC, and the MCS contractors to work out a draft design of an NMOP prior authorization process that the committee could review. This issue is resolved by the restructuring of the NMOP formulary, which includes a category of drugs that are subject to prescribing guidelines/prior authorization.

G. NMOP quantity limitations for ophthalmics and topicals (specifically urea 40% cream): The subcommittee that was appointed to review quantity limitations for migraine drugs will also develop recommendations for the P&T committee regarding quantity limitations for ophthalmics and topicals. (OPEN)

9. NEW BUSINESS: Contracting update

A. Insulin: Pre-solicitation conferences with the pharmaceutical companies are scheduled for 18 and 20 May 99. The solicitation will probably be issued within a week to 10 days after pre-solicitation conferences are completed. This is a joint VA/DoD contracting initiative.

B. Statins: DSCP recently completed discussions with the offerors. The deadline for final proposal revisions is 21 May 99. Target date for awarding the contract is 11 Jun 99.

C. Proton pump inhibitors: The solicitation was issued on 7 May 99 and closes on 10 Jun 99.

D. Lisinopril: The solicitation closes on 21 May 99.

E. Blood glucose test strips: The PEC recommends discontinuation of the current contracting initiative to select a single blood glucose test strip for a closed class on the BCF. Contracting initiatives are taking much longer to complete than originally anticipated. Some MTFs are reluctant to adopt the test strip that is currently on the BCF (Precision QID) because they do not want to switch patients twice in the event that a contract is awarded for a different test strip. Given the number of contracting initiatives that DSCP is already working on, a contract for blood glucose test strips would very likely take 8 to 12 months to complete. It is unreasonable to hold up MTF formulary decisions for that length of time. Committee decision: **Discontinue the current blood glucose test strip contracting initiative. Precision QID remains as the blood glucose test strip in an open class on the BCF.**

F. Selective serotonin reuptake inhibitors (SSRIs): At the Nov 98 meeting the committee concurred with a proposal to select one SSRI for an open class on the BCF. It was anticipated that blanket purchase agreements or DAPA incentive agreements would be established to facilitate the selection of an SSRI for an open class on the BCF, but such

agreements have not been established. The committee intends to select one SSRI for an open class on the BCF at the Aug 99 meeting.

G. Warfarin: At the Nov 98 meeting the committee removed the Coumadin brand only designation from the BCF with the intent of pursuing a sole source contract for a single brand of warfarin. Price competition appears to be increasing in the warfarin market. Increased price competition may diminish the need to pursue a sole source contract.

10. ADJOURNMENT: The meeting adjourned at 1400 hours. The next meeting will be held on 13 August 1999 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas, beginning at 0800 hours. All agenda items are to be submitted to the DoD PEC no later than 16 July 1999.

<signed>	<signed>
DANIEL D. REMUND COL, MS, USA Co-chairman	TERRANCE EGLAND CDR, MC, USN Co-chairman

Appendix A: NMOP Formulary

Drugs that are covered:

- All non-injectable prescription drugs that are *not* excluded. (Excluded drugs are listed in the Excluded Drugs category.)
- Injectable drugs listed in the Covered Injectable Drugs category
- Non-prescription drugs or products listed in the Covered OTC Drugs/Products category

Excluded Drugs

Drug Classes Excluded for Active Duty Members Only:
- Amphetamines
- CNS stimulants
- Controlled substances in Schedules II, III, IV, V

Excluded Drug Classes:
- Anabolic steroids
- Contraceptive creams, foams, implants, injections, jellies
- Immune globulins
- Immunizations
- Injectable drugs (unless listed in the Covered Injectable Drug category)
- Legend prenatal vitamins for males, and females age 46 and over
- Legend vitamins
- Over-the-counter (OTC) drugs (unless listed in the Covered OTC Drugs/Products category)
- Smoking deterrents
- Vaccines

Exclusions by Drug Use:
- Drugs for cosmetic use as a result of the aging process (e.g., tretinoin cream (Renova)) or whose sole use is to stimulate hair growth [e.g., topical minoxidil (Rogaine), finasteride (Propecia)].
- Drugs for investigational use
- Drugs for obesity and/or weight reduction

Specific Drug Exclusions:
- Clozapine (Clozaril)
- Enoxaparin (Lovenox)
- Quinine
- Thalidomide (Thalomid)
- Tretinoin (Retin-A) age 36 and over

New FDA-approved drugs:
- Excluded until reviewed by the DoD P&T Committee (will be listed in the Drugs Pending P&T Committee review category—to be updated as new drugs are approved by the FDA)

Drugs Pending P&T Committee Review

- Cilostazol (Pletal)

Covered Injectable Drugs*

- Alprostadil (Caverject, Muse) intracavernosal injection
- Antihemophilic Factor VIII
- Antihemophilic Factor IX Complex
- Calcitonin salmon injection
- Cyanocobalamin injection
- Epoetin alfa, recombinant (Epogen, Procrit)
- Filgrastim (Neupogen) injection
- Glatiramer acetate (Copaxone) injection
- Glucagon
- Goserelin acetate (Zoladex) implant syringe
- Insect Sting Treatment Kit
- Insulin
- Insulin analog (Humalog) injection
- Interferon Alpha (Infergen, Roferon-A, Intron A, Rebetron)
- Interferon Beta (Avonex, Betaseron)
- Interferon Gamma-1b (Actimmune)
- Leuprolide (Lupron) depot and subcutaneous injections
- Menotropins (Repronex) injection
- Octreotide (Sandostatin) injection
- Sargramostim (Leukine) injection
- Somatrem (Protropin)
- Somatropin (Humatrope)
- Sumatriptan (Imitrex) injection
- Urofollitropin (Fertinex) injection

**** many of these agents currently have quantity restrictions***

Covered OTC Drugs/Products

- Glucose Test Strips
- Insulin and Insulin syringes
- Lancets
- Niacin (for antilipemic therapy)
- Alcohol swabs, needles and syringes (for injectable drugs dispensed for home injection only)

Drugs Subject to Practice Guidelines/Prior Authorization
• Celecoxib (Celebrex) • Etanercept (Enbrel) • Sildenafil (Viagra)

Non-Preferred Drugs and Preferred Alternatives	
Non-Preferred	**Preferred**
Astemizole (Hismanal)	➢ **Cetirizine (Zyrtec)** **Fexofenadine (Allegra)** **Loratadine (Claritin)**
Diclofenac extended release (ER) (Voltaren XR)	➢ **Diclofenac (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Salsalate (generic)** **Piroxicam (generic)**
Diltiazem ER (Cardizem CD) Diltiazem ER (Dilacor XR) Diltiazem ER (Diltia XT) Diltiazem ER (Diltiazem XR)	➢ **Diltiazem ER (Tiazac)**
Etodolac ER (Lodine XL)	➢ **Etodolac (generic)** **Ibuprofen (generic)** **Naproxen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Famciclovir (Famvir)	➢ **Acyclovir (generic)**
Nabumetone (Relafen)	➢ **Salsalate (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Naproxen sodium ER (Naprelan)	➢ **Naproxen (generic)** **Ibuprofen (generic)** **Salsalate (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Nifedipine ER (Procardia XL)	➢ **Nifedipine ER (Adalat CC)**
Oxaprozin (Daypro)	➢ **Salsalate (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Oxybutynin ER (Ditropan XL)	➢ **Oxybutynin (generic)**
Tolterodine (Detrol)	➢ **Oxybutynin (generic)**
Valacyclovir (Valtrex)	➢ **Acyclovir (generic)**
Zileuton (Zyflo)	➢ **Montelukast (Singulair)**

	Zafirlukast (Accolate)

Appendix B: Summary of efficacy, safety and cost issues associated with celecoxib (Celebrex; Searle/Pfizer)

1. Celecoxib does not appear to be any more or any less effective than other non-steroidal anti-inflammatory drugs (NSAIDs) in treating the symptoms of osteoarthritis (OA) or rheumatoid arthritis (RA).
2. The potential benefit of a cyclooxygenase-2 (COX-2) inhibitor such as celecoxib is primarily due to the lack of inhibition of cyclooxygenase-1 (COX-1) at therapeutic doses. Lack of COX-1 inhibition is mechanistically related to a potential decrease in the risk of GI adverse events (ulceration, bleeding, and perforation). Celecoxib lacks the platelet effects associated with other NSAIDs. Celecoxib does not appear to differ from other NSAIDs in terms of renal adverse effects or use during pregnancy.
3. Labeling for celecoxib includes the same warnings about increased risk of adverse gastrointestinal (GI) events as other NSAIDs. During its first three months on the market, 10 deaths and 11 serious gastrointestinal events (bleeding or ulcer) were reported in patients receiving celecoxib. This must be considered in the context of the number of patients who have been exposed to celecoxib during this period, as well as the expected background rate of adverse GI events in patients not exposed to NSAIDs.
4. Trials with celecoxib have shown a significant reduction in the incidence of endoscopically detected ulcerations compared to other NSAIDs. The correlation between endoscopic ulcers and actual GI adverse events is unclear. Premarketing trials with celecoxib were not designed to collect outcomes data on actual events, and no firm conclusions can be drawn from these results.
5. Overall, about 10% of patients (20.7 million) in the U.S. have OA; about 1% (2.1 million) have RA. Patients with RA are at greater risk for NSAID-induced adverse events because they are older, receive higher NSAID doses, and are more likely to be receiving other medications that increase risk.
6. For patients with rheumatoid arthritis (RA), the annual rate of GI hospitalizations is about 1.46% in patients taking NSAIDs compared to 0.27% in patients not taking NSAIDs. Number-needed-to-harm (NNH) = 84. For patients with osteoarthritis (OA), the annual rate of GI hospitalizations is about 0.73% in patients taking NSAIDs compared to 0.29% in patients not taking NSAIDs. NNH = 227.
7. *If the assumption is made that the rate of GI adverse events in patients receiving celecoxib is equal to the rate in patients not receiving NSAIDs,* 84 RA patients or 227 OA patients (or an even greater number of patients in the general patient population) would have to be treated with celecoxib for 1 year in order to avert 1 GI hospitalization. Treating 84 RA patients with celecoxib would increase annual drug costs by approximately $41,403 compared to treatment with conventional NSAIDs. Treating 227 OA patients with celecoxib would increase annual drug costs by approximately $111,888 compared to treatment with conventional NSAIDs. (Note: these estimates are based on the mean daily cost for NSAIDs in the National Mail Order Pharmacy (NMOP) program during calendar year 1998 (about $0.71) and an estimated daily cost for celecoxib of $2.06. Facilities with a lower mean daily cost for NSAIDs would experience greater increases in drug costs if patients were switched from current NSAID therapy to celecoxib.)
8. Use of COX-2 inhibitors such as celecoxib may decrease costs by reducing the number of patients who require concomitant treatment with misoprostol, H2 blockers, or proton pump inhibitors (PPIs). It is difficult to quantify the number of patients who could successfully be taken off H2 blockers or PPIs, since patients may require treatment with such agents for conditions that are independent of NSAID use.
9. Risk factors for increased risk of NSAID-induced GI adverse events include previous history of GI complications, age, concomitant use of corticosteroids and anticoagulants, high doses of NSAIDs, and general health status.
10. A prescribing guideline designed to target the use of celecoxib to patients at high risk for a GI adverse event would minimize the number of patients who must be treated to avert such an event and maximize the *potential* safety benefit associated with celecoxib. It must be noted that an actual reduction in the rate of GI adverse events with celecoxib has not yet been demonstrated in clinical trials. Outcomes studies to address this question are currently in progress.

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MCCS-GPE 5 February 1999

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with Health Affairs policy 98-025, a meeting of the DoD P&T committee convened at 0800 hours on 5 February 1999, at the Skyline office complex in Falls Church, Virginia.

2. MEMBERS PRESENT:

COL William D. Strampel, MC	Co-chairman
COL Daniel D. Remund, MS	Co-chairman
COL Rosa Stith, MC	Army Representative
LTC Judith O'Connor, MC	Army Representative
Ms. Danielle Doyle, DAC	Army Representative
CDR Terrance Egland, MC	Navy Representative
LCDR Denise Graham, MSC	Navy Representative
LCDR John Tourtelot, MC	Navy Representative (alternate)
LtCol John R. Downs, MC	Air Force Representative
LtCol William Sykora, MC	Air Force Representative
LtCol (Sel) Greg Russie, BSC	Air Force Representative
LCDR Pamela Stewart-Kuhn	Coast Guard Representative (alternate)
Capt Debra Parrish, BSC	DSCP Representative
Mr. John Lowe	VA Representative
Mr. Kirby Davis	Anthem Alliance Representative
Ms. Ray Nan Berry	Foundation Health Representative
Mr. William Hudson	Humana, Inc., Representative
Mr. Ron McDonald	Sierra Military Health Service Representative
Mr. Gene Lakey	TriWest Representative

3. OTHERS PRESENT:

CAPT (Sel) Charlie Hostettler	DoD Pharmacy Program Director
MAJ Mickey Bellemin, BSC	DSCP
Mr. Tom Kellenberger	Merck-Medco Representative
Ms. Shana Trice, DAC	Army

4. ADMINISTRATIVE ISSUES:

A. New attendees were introduced:

(1) CAPT (Sel) Charlie Hostettler - DoD Pharmacy Program Director
(2) LCDR John Tourtelot - Pharmacist/Endocrinologist, Bethesda Naval Medical Center

B. COL Strampel stated that this is his last duty day and that he is relinquishing his co-chair duties. MAJ Steve Humburg, MC, USAF, will replace COL Strampel as the physican representative from the TRICARE Management Activity (TMA) to the DoD P&T Committee.

C. The DoD P&T committee charter states that the physician co-chair is to be selected from within the membership. The committee selected CDR Terry Egland as the physician co-chair.

D. An audio recording of the committee meeting is being made to assist in preparation of the minutes. The tape will be destroyed after the minutes are written.

5. OLD BUSINESS:

A. The committee reviewed the minutes from the 13 November 1998 meeting and accepted them as written.

B. All financial disclosure statements have been submitted.

C. Alternate P&T members have still not been identified for the Army. (OPEN)

D. Potential limitations on fertility drugs in the NMOP: The PEC reviewed the medical literature and found studies showing modest reductions in the success rate with fertility drugs as the number of treatment cycles increased. However, there is no precipitous drop in the success rate that would provide a definitive clinical rationale for limiting treatment to a specific number of cycles. Guidelines and criteria developed by Merck-Medco for other health plans suggest continuation of drug therapy for up to six months. Continuation of therapy beyond six months is typically handled on a prior authorization basis. The NMOP contract does not currently provide a mechanism for prior authorization.

The committee decided that more information is needed about fertility drug usage in the NMOP before the committee is willing to explore the establishment of a prior authorization process. The NMOP is to provide information about the number of patients treated, the distribution of those patients according to number of treatment cycles, and the drug therapy costs. (OPEN)

E. Migraine therapy: The clinical practice guideline group confirmed that it does not plan to develop a guideline for migraine therapy. Capt Parrish stated that the NMOP already has migraine product quantity limits that are similar to what Merck-Medco recommends for other health care plans. These quantity limits have not engendered large numbers of patient complaints. Some committee members commented that the NMOP quantity limits are more generous than the quantity limits typically established at MTF pharmacies. Capt Parrish remarked that patient complaints more frequently involve prescriptions for unapproved uses of the drugs (e.g. sumatriptan 50 mg twice daily for a 90-day supply).

   The committee concluded that it is unclear whether a problem actually exists regarding migraine therapy in the NMOP. The NMOP is to provide drug usage data for migraine therapy and include, if possible, an assessment of the extent to which patients obtain migraine medications simultaneously from the NMOP, retail network and MTF pharmacies. (OPEN)

F. Sildenafil (Viagra) policy: COL Strampel stated that a change in the policy or publication of an implementation plan to address flaws in the policy are unlikely to occur. The PEC developed a one-page guideline sheet for Merck-Medco to fax to prescribers so that they can certify that the clinical guideline has been met before Viagra is dispensed. The NMOP has not started to use the guideline sheet. The delay in implementation is presumed to be due to an ongoing legal review of the document by Merck-Medco.

G. Oral contraceptives: Capt Parrish stated that more companies have agreed to offer the same prices for different size packs of oral contraceptives (e.g., 21-, 28-day packs). Sufficient progress has been made to close out this issue.

H. Impact of worldwide flu shots: This item was in reference to a paper that appeared just prior to the last meeting indicating that a push to immunize children against the flu might yield even more benefit than that realized from immunizing older people. This issue is not within the purview of the committee.

6. NEW BUSINESS: FDA priority review drugs—automatic consideration for the BCF and NMOP

   A. **None of the drugs discussed below were added to the BCF** because they are not essential for every MTF to have on their formulary to meet the primary care needs of patients. Committee members were reminded of the four categories that a drug may occupy regarding availability through the NMOP:

(1) **Drug is on the NMOP preferred drug list (PDL)**.

(2) **Drug is not on the NMOP PDL but is "mapped" to one or more drugs that are on the NMOP PDL.** Prescriptions for drugs in this category are filled by the NMOP when none of the drugs on the NMOP PDL can satisfy the clinical needs of the patient. Mapping associates a drug that is not on the NMOP PDL with one or more drugs that are on the NMOP PDL. When a prescription is received for a drug in this category, the NMOP will contact the prescriber to attempt to change the prescription to a drug that it is mapped to on the NMOP PDL. If the prescriber determines that none of the drugs on the NMOP PDL will meet the clinical needs of the patient, the prescription will be filled as originally written.

(3) **Drug is not on the NMOP PDL and is not mapped to a drug on the NMOP PDL, but prescriptions are filled by the NMOP.** Very few drugs will be included in this category. These drugs are deemed to be inappropriate for designation as "preferred" drugs, and they cannot be mapped to acceptable substitutes on the NMOP PDL. Nevertheless, these drugs may be beneficial for some patients and do not appear to present unacceptable safety risks. Prescriptions for drugs in this category will be filled without contacting the prescriber. Papaverine is an example of a drug in this category (see discussion in paragraph 8G).

(4) **Drug is excluded from the NMOP.** Prescriptions will not be filled for drugs that are excluded from the NMOP. The statement of work for the NMOP contract identifies a number of drugs that are excluded from the NMOP. The DoD P&T Committee may also exclude drugs from the NMOP. All newly approved drugs are automatically excluded from the NMOP unless and until the DoD P&T Committee places the drug in one of the three preceding categories.

B. Valrubicin (Valstar) solution is a chemotherapeutic agent that is instilled into the urinary bladder once a week for treatment of urinary carcinoma. **Exclude valrubicin from the NMOP** because it requires special handling as a cytotoxic agent and must be administered using aseptic technique and under the supervision of a physician experienced in the use of intravesical chemotherapeutic agents.

C. The discussion of valrubicin led to a discussion about the status of leuprolide depot (Lupron) injection, which is on the NMOP PDL, and leuprolide acetate for subcutaneous injection, which is not on the NMOP PDL. The leuprolide depot injection is known to be given at home. The committee decided to retain leuprolide depot injection on the NMOP PDL and **add leuprolide subcutaneous injection to the NMOP PDL.**

D. Octreotide acetate depot injection (Sandostatin LAR) is a long-acting intramuscular injection for the reduction of growth hormone and IGF-1 in acromegaly; the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome; and the

treatment of profuse watery diarrhea associated with VIPomas (vasoactive intestinal peptide secreting tumors). Octreotide subcutaneous injection is listed on the NMOP PDL. **Exclude Sandostatin LAR from the NMOP** because it is an intragluteal injection that is not designed for self-administration.

E. Lamivudine (Epivir-HBV) tablets and oral solution are indicated for the treatment of adults with chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. Epivir-HBV should not be used in HIV-infected patients because it contains a lower dose of lamivudine than is required for treatment of HIV infection. Testing for HIV is advised prior to beginning treatment with the drug and periodically during treatment. **Add Epivir-HBV to the NMOP PDL** because of its clinical effectiveness for the treatment of hepatitis B and because other dosage forms of lamivudine are on the NMOP PDL.

F. Abacavir (Ziagen) is a nucleoside analogue reverse transcriptase inhibitor for combination treatment of HIV_1 infection in adults and pediatric patients older than 3 months of age. Prescriptions for abacavir are already being filled through the NMOP based on the committee's previous decision that HIV antiretrovirals would automatically be added to the NMOP PDL. A question arose about whether the "automatic addition" policy for antiretrovirals meant that the NMOP should start filling prescriptions for the drug even before the committee formally approved the addition of the drug to the NMOP PDL. The committee confirmed the **addition of abacavir to the NMOP PDL** and decided that in the future a committee co-chair should give the NMOP interim approval to fill prescriptions for antiretrovirals until the committee formally approves the addition of the drug to the NMOP PDL.

G. Celecoxib (Celebrex), commonly known as a COX-2 inhibitor, is indicated for relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis. At least one other COX-2 inhibitor is expected to enter the market in the near future. Celecoxib does not appear to be any more effective than NSAIDs for osteoarthritis and adult rheumatoid arthritis. Clinical trials comparing celecoxib to naproxen or ibuprofen show that celecoxib is associated with a lower incidence of endoscopically determined ulcerations. However, definitive evidence that celecoxib reduces the incidence of clinically relevant gastrointestinal events is not yet available. The official labeling for celecoxib includes warnings against gastrointestinal side effects similar to those for NSAIDs. Celecoxib is similar in cost to brand name NSAIDs, but is many time more expensive than generic NSAIDs. Prescribing guidelines will likely be required to target usage of COX-2 inhibitors for patients requiring chronic NSAID therapy who are at increased risk for gastrointestinal problems. The minimal amount of available information concerning the actual clinical benefit of celecoxib makes it difficult to develop prescribing guidelines. The committee concluded that there is not a clear imperative to make celecoxib immediately available through the NMOP. The committee **tabled consideration of celecoxib until the next meeting** when more information will hopefully be available to more clearly quantify the clinical benefit that this agent potentially offers. **In the interim, celecoxib is**

excluded from the NMOP. The committee also suggested that MTFs might want to provide this drug through the special order process rather than add it to their formularies at this time. (OPEN)

H. The discussion of celecoxib led to a discussion about the presence of brand name NSAIDs on the NMOP PDL. The NMOP began in October 1997 with a closed formulary that did not include brand name NSAIDs. Brand name NSAIDs were added to the closed NMOP formulary because it was thought that many patients would obtain brand name NSAIDs through the retail network pharmacies at a higher cost to the government if they were not included on the NMOP formulary. The closed NMOP formulary changed to the NMOP PDL in April 1998 and brand name NSAIDs remained on the NMOP PDL. It was suggested that brand name NSAIDs should now be removed from the NMOP PDL and mapped to the generic NSAIDs because brand name NSAIDs do not offer incremental clinical benefits that are commensurate with their high cost compared to generic NSAIDs. The committee tabled this issue until the next meeting in order to consider the brand name NSAIDs and COX-2 inhibitors in an integrated fashion. (OPEN)

7. NEW BUSINESS: BCF Issues

A. Oxybutynin extended release (Ditropan XL): Oxybutynin oral is listed on the BCF, so Ditropan XL would automatically be included on the BCF unless it is specifically excluded. The committee decided to **exclude Ditropan XL from the BCF** because it is unlikely that the incremental clinical benefit will counterbalance the fact that it is more than four times more costly than the immediate release form of oxybutynin. The committee also decided to **map Ditropan XL to immediate release oxybutynin on the NMOP**, which is the same decision that was made at the last meeting for tolterodine (Detrol).

B. Timolol maleate gel (Timoptic XE): Timolol ophthalmic solution is listed on the BCF. The committee decided to **exclude Timoptic XE from the BCF** because it is unlikely to offer sufficient incremental clinical benefit to offset the fact that it is seven to nine times more costly than timolol ophthalmic solution.

C. Triamcinolone oral inhaler (Azmacort): A recent substantial increase in the DAPA price for Azmacort (raised from $7.95 to $12.90 per inhaler) caused the committee to consider the removal of Azmacort from the BCF. The PEC was recently informed that the manufacturer will reduce the price to $9.60 per inhaler effective 1 Mar 99. The committee voted to **table this issue**. The committee wants to be more certain about the price and also wants to ensure that the BCF adequately supports the asthma/COPD treatment guideline that is being developed by the DoD/VA Clinical Practice Guideline Workgroup. (OPEN)

D. Verapamil dosage forms: Verapamil oral is currently listed on the BCF. The committee decided to specify that the BCF listing for verapamil oral includes only the dosage forms

for which generic equivalent products are available. Generic equivalent products are available for the immediate release tablets (e.g. Calan, Isoptin, and others) and the sustained release tablets (e.g. Calan SR, Isoptin SR and others). All other forms of verapamil are excluded from the BCF (such as Verelan, Verelan PM and Covera HS).

E. "Brand Name Only" items: "A" rated generics are available for phenytoin and carbamazepine, but these drugs are still designated as "brand name only" on the BCF. The committee supports the position of the FDA that an "A" rated generic drug is both bioequivalent and therapeutically equivalent to the innovator (brand name) drug. The committee voted to **remove the brand name only designation for phenytoin and carbamazepine on the BCF**. The committee further stipulated that only "A" rated generic equivalent products should be substituted for the brand name products. The NMOP must comply with state laws and regulations that govern the substitutability of generic drugs, so the committee cannot necessarily apply the same policy to the NMOP. Capt Parrish stated that the NMOP operates under New Jersey regulations that currently do not allow generic substitution for phenytoin and carbamazepine.

F. Montelukast (Singulair): Portsmouth Naval Medical Center requested the addition of montelukast to the BCF and NMOP PDL. The BCF does not include any leukotriene receptor antagonists. Zafirlukast (Accolate) is on the NMOP PDL. Montelukast is not on the NMOP PDL but is mapped to zafirlukast. Montelukast is indicated for use in patients as young as six years of age while zafirlukast is only approved for patients aged 12 years and older. Montelukast may also cause less diarrhea, can be given without regard to meals, and is a once-daily agent. The committee **did not add montelukast to the BCF** because it is not an agent that every MTF should be required to have on its formulary. The committee noted that excluding montelukast from the BCF does not preclude any MTF from having montelukast on its formulary. The committee **added montelukast to the NMOP PDL** because it offers clinical advantages commensurate with the higher cost ($1.39 per day for montelukast versus $1.07 per day for zafirlukast). Additionally, Capt Parrish reported that the switch rate for monelukast prescriptions in the NMOP is low, and that the NMOP fills more prescriptions for montelukast than anyother agent not listed on the NMOP PDL.

8. NEW BUSINESS: Other NMOP Issues

A. Report on top "mapped" items: Capt Parrish identified the ten mapped agents for which the NMOP received the most prescriptions. Each time a prescription is received for a mapped agent, the NMOP calls the prescriber to request a change to an agent that is on the NMOP PDL. The "switch rates" identified below refer to the percentage of prescriptions that are switched to agents that are on the NMOP PDL and the number of prescriptions were received over a 6-month period. The committee changed the NMOP status of the various drugs as described below. [Note: In order to make more informed decisions about the NMOP PDL, the committee requested that more data be provided in the future about what prescriptions are being switched to and the relative efficacy, cost

and safety of the various agents.]

(1) Montelukast (Singulair): decision already made to **add to NMOP PDL**.

(2) Glimepiride (Amaryl): Received 912 prescriptions and attained a 15% switch rate. Information on the agents these prescriptions were switched to is not available (i.e. whether a change was made to Glucotrol XL or to generic sulfonylureas). The committee **added glimepiride to the NMOP PDL** on the supposition that glimeperide prescriptions received by the NMOP would most likely be switched to Glucotrol XL, which is more expensive than glimeperide.

(3) Loratadine and pseudoephedrine (Claritin-D 12-Hour and Claritin-D 24-Hour) tablets: The NMOP PDL currently includes fexofenadine (Allegra) and loratadine (Claritin), but does not include the dosage forms that combine these agents with pseudoephedrine. The committee **added Claritin-D 12-Hour, Claritin-D 24-Hour, and Allegra-D tablets to the NMOP PDL** because they cost the same or only slightly more than the plain loratadine or fexofenadine dosage forms.

The committee also considered a request from Walter Reed Army Medical Center (WRAMC) to add cetirizine (Zyrtec) to the NMOP PDL to support WRAMC's new guidelines which may increase the number of cetirizine prescriptions that are submitted to the NMOP. WRAMC is implementing a rhinitis clinical practice guideline that identifies cetirizine as the lead antihistamine. WRAMC submitted documentation indicating that cetirizine (1) is slightly less expensive than other "non sedating" antihistamines and less than half as expensive if tablets are broken in half, (2) has a pediatric indication down to age 2 and is nonsedating at the 5 mg dose in the under 12 age group, and (3) enables WRAMC to comply with the new Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. The **committee added cetirizine to the NMOP PDL**. The committee also decided that astemizole (Hismanal) should remain mapped, and that the mapping should be expanded to include the newly added agents.

(4) Tamsulosin (Flomax): **Leave tamsulosin mapped to other alpha-1-adrenergic blockers**.

(5) Norgestimate and ethinyl estradiol (Ortho Tri-Cyclen): Received 754 prescriptions. **Add Ortho Tri-Cyclen to the NMOP PDL**.

(6) Torsemide (Demadex): Received 736 prescriptions and attained a 22% switch rate. The committee decided to leave **torsemide mapped to other diuretics** since most of the switches were probably to a generic furosemide at significantly lower cost.

(7) Mometasone nasal spray (Nasonex): Received 404 prescriptions and attained an 81% switch rate. The committee **tabled consideration of this agent** until prices for agents in this category are known with greater certainty. (OPEN)

(8) Irbesartan (Avapro): Attained a 55% switch rate. **Leave irbesartan mapped** to other angiotensin II receptor antagonists.

(9) Bisoprolol/hydrochlorothiazide (Ziac): Received 628 prescriptions and attained a 12% switch rate. It was not clear to which drugs the prescriptions were being switched. The difficulty in recommending an alternative for a combination product such as Ziac was discussed. The committee voted to **add Ziac to the NMOP PDL**.

(10) Insulin analog injection (Humalog): Received 362 prescriptions with a 0% switch rate. The committee voted to **add Humalog to the NMOP PDL**.

B. Handling of high-dollar items in NMOP: The committee considered a proposal to establish an NMOP prior authorization process that is accomplished by the entity (MTF or MCS contractor) that is at financial risk for the prescription. The committee asked the NMOP COTR, the PEC, and the MCS contractors to work out a draft design of an NMOP prior authorization process that the committee could review prior to forwarding any recommendations to TMA or Health Affairs. (Open)

C. Quantity limits on eye drops: The NMOP computer system allows large quantities of ophthalmic drops for allergic conditions to be dispensed based on the maximum possible doses per day. Until the computer system can be modified to alleviate this problem, Capt Parrish sought guidance from the committee on reasonable quantity limitations. The committee decided to limit quantities for ophthalmic drops for allergic conditions to a maximum of two bottles per month or six bottles per three months. The committee asked the NMOP COTR to provide a list of the agents that will be subject to this limitation. The NMOP COTR will also identify any other ophthalmic agents that should be considered for quantity limitations. (OPEN)

D. Leflunomide (Arava): A decision on leflunomide was tabled at the last meeting. The NMOP PDL includes six other disease-modifying antirheumatic drugs (DMARDs): methotrexate, sulfasalazine, hydroxychlorquine, auranofin, penicillamine, and azathioprine. Drug acquisition cost for one year of therapy with leflunomide would be about $1900. Other DMARDs are less expensive, but mapping leflunomide to other DMARDs would likely result in few switches to agents on the NMOP PDL. Leflunomide appears to represent a therapeutic advance in a relatively well defined population of patients and may serve as an alternative to methotrexate. The committee voted to **add leflunomide to the NMOP PDL**. **Leflunomide was not added to the BCF**.

E. Urea 40% topical (Carmol-40 and others): This is a topical agent used as a moisturizing agent for severely dry skin or under an occlusive dressing to remove diseased nails. The committee **approved addition of this agent to the NMOP PDL**. The committee did not specify a quantity limitation, but the NMOP contracting

officer's technical representative (COTR) is to assess the need for a quantity limitation and report back to the committee. (Open)

F. Quinine: Quinine has historically been used to treat night leg cramps, although this has never been an approved indication. In 1994 the FDA ordered a halt to the marketing of over-the-counter (OTC) quinine sulfate for night leg cramps based on its serious risks. In 1995 the FDA ordered a halt to the marketing of prescription quinine for this use because, even under a physician's care, the risks outweigh any possible benefits. Quinine is now available only as a prescription drug for the second line treatment of malaria. The committee voted to **exclude quinine from the NMOP** in order to preclude inappropriate use of the drug for night leg cramps. The relatively small number of patients who require quinine for second line treatment of malaria can obtain the medication through MTF pharmacies or retail network pharmacies. No new prescriptions will be filled at the NMOP, but existing refills will be honored.

G. Papaverine: Papaverine is a pre-1962 drug that is classified as probably effective for the relief of cerebral and peripheral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias. Given the limited evidence of clinical effectiveness, the committee does not want to list papaverine on the NMOP PDL. Mapping papaverine to other agents is not practical because there is not a specific agent to suggest as an alternative to papaverine. The committee decided that **papaverine will not be on the NMOP PDL and will not be mapped, but prescriptions for papaverine will continue to be filled by the NMOP.**

H. Tobramycin nebulizer solution (TOBI): This is the only nebulizer solution available for treatment of pseudomonas infection in cystic fibrosis patients. A number of other nebulizer solutions are currently supplied by the NMOP. The committee voted to **add TOBI to the NMOP PDL**.

I. Ofloxacin (Floxin) and grepafloxacin (Raxar) package sizes: Capt Parrish reported that special dose packs has recently been introduced for these agents. The prices of these dose packs are very high in relation to simply dispensing the equivalent number of tablets. In contrast, the Zithromax "Z-pak" is less expensive for the NMOP to dispense than 6 tablets. The committee decided to **exclude the ofloxacin and grepafloxacin dose packs from the NMOP.** The NMOP is to offer to fill prescriptions for ofloxacin and grepafloxacin dose packs with the equivalent number of tablets from traditional packaging.

The committee also authorized the NMOP to routinely exclude other more expensive special packaging from coverage through the NMOP when the special packaging does not offer sufficient incremental benefit to justify a higher cost. The general rule is that the substitution must be less expensive than the special packaging and result in no difference in the education or the therapy received by the patient. For example, it would not be feasible to substitute for something like a Medrol dose-pak because it

would be difficult to explain the dosing regimen to patients. The NMOP COTR will routinely report such exclusions to the committee for its concurrence.

J. Nitroglycerin patches: A review of DAPA prices revealed that Nitrodur is significantly less expensive at $.26 per patch than other brands of nitroglycerin patches. The Nitrodur brand offers an extensive array of patch strengths. The committee voted to **specifically list only the Nitrodur brand of nitroglycerin patch on the NMOP PDL. All other brands of nitroglycerin patches will be mapped to the Nitrodur brand**.

K. Antivirals for herpes: Acyclovir and valacyclovir (Valtrex) are currently listed on the NMOP PDL, while Famvir (famciclovir) is mapped to these agents. All three agents are indicated for the treatment of herpes zoster (shingles), recurrent genital herpes (herpes simplex), and suppression of recurrent genital herpes. Famciclovir is indicated for cold sores in HIV patients. Acyclovir is indicated for the treatment of varicella (chicken pox). Depending on the indication, famciclovir and valacyclovir range from three to seventeen times more expensive than acyclovir. The substantially greater cost of famciclovir and valacyclovir appears to outweigh any incremental clinical benefit they might offer over acyclovir. The committee voted to **remove valacyclovir (Valtrex) from the NMOP PDL and to map both valacyclovir and famciclovir to acyclovir** as the more cost-effective alternative. Merck-Medco will place calls to physicians to encourage the use of acyclovir when new prescriptions are submitted for famciclovir or valacyclovir. Existing refills for valacyclovir and famciclovir will be honored. The rate of switching from these agents to generic acyclovir will be monitored by the NMOP.

L. Enbrel (Etanercept): Etanercept is indicated for reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Etanercept can be used in combination with methotrexate when patients have an inadequate response to methotrexate alone. Etanercept is given via subcutaneous injection twice weekly and is designed and packaged with necessary supplies for self-administration. It has been shown to be effective for rheumatoid arthritis; however, little evidence is available on long-term use and symptoms return promptly after discontinuation. The drug cost for one year of therapy is approximately $8,500.

Given the extremely high cost of etanercept, it may be important to establish a prescribing guideline to ensure that it is used only for patients for whom it is clearly indicated. Information is also needed regarding the manufacturer's shipping policies and the necessity for shipping the drug on dry ice. The committee agreed to **table a decision on etanercept** to allow some time to explore the development of a prescribing guideline and to clarify the logistical issues associated with mailing the drug. **In the interim, etanercept is excluded from the NMOP.** (OPEN)

M. Urine glucose test strips and urine ketone test strips: The committee did not think these agents should be added to the NMOP PDL. Mapping urine glucose test strips and urine ketone test strips to other agents would be nonsensical. The committee decided that **urine glucose test strips and urine ketone test strips will not be added to the NMOP PDL and will not be mapped, but prescriptions for these agents will be filled by the NMOP.**

N. Niacin for antilipemic therapy: Various barriers work against the provision of niacin through the NMOP. The NMOP does not provide over-the-counter (OTC) items except for insulin and insulin syringes. The NMOP is also prohibited from providing OTC or prescription vitamins, with the exception of prescription multivitamins with folic acid for women ≤ 45 years of age. Capt Parrish stated that the NMOP is not permitted to dispense a niacin product that requires a prescription if the same dosage form and strength is also available OTC. Prescription dosage forms and strengths of niacin are generally also available as OTC products. The majority of the committee members agreed that niacin for antilipemic therapy should be available through the NMOP. The committee tabled this issue to allow consultation with TMA officials about how niacin can be made available for antilipemic therapy through the NMOP. (Open)

9. NEW BUSINESS: Other Issues

A. A managed care support contractor representative asked the committee to consider two proposals: 1) that the NMOP supply blood glucose testing devices and syringes for covered injections, and 2) that the NMOP waive additional co-pays for supplies when dispensed with a covered injection. These proposals are apparently related to a pending managed care support contract modification that specifies waiving of the co-pay for supplies when dispensed with the covered injection.

1. The NMOP statement of work limits authorized supplies to "insulin and related supplies limited to disposable insulin syringes and consumable products intended for home testing for glucose in the blood or urine." Syringes for covered injections other than insulin are not included in the NMOP statement of work. Blood glucose meters are not consumable products, so they are not included in the NMOP statement of work. The committee does not have the authority to unilaterally alter the NMOP statement of work.

2. The committee does not have the authority to waive the co-pays that are established in the NMOP statement of work.

B. BCF limitations on glucose test strips: Brooke Army Medical Center and Wilford Hall Air Force Medical Center (BAMC/WHMC) requested that the committee reconsider the BCF limits on glucose test strips. The BCF limits glucose test strips to a maximum of 100 per 90 days for non-insulin dependent diabetics and 400 strips per 90 days for diabetics who use insulin. The BCF does not limit quantities for any BCF agents other

than glucose test strips. BAMC/WHMC presented concerns about pregnant patients or patients using an insulin pump, who may use up to 7 strips per day, and patients on oral medications who may want or need to test more often than once per day. It was pointed out that it should be possible for facilities to have patients bring in their monitors, download, see what they are using, and supply appropriate amounts. The committee agreed that individual MTFs should be able to establish their own quantity limitations. The committee voted to **remove the quantity limitations on blood glucose test strips from the BCF**. No change was made to the quantity limits for the NMOP.

C. Application of quantity limits in NMOP to prescriptions filled in retail network pharmacies: This issue requires action by TMA and/or Health Affairs and is beyond the purview of the committee.

D. Contracting issues: Contracting issues were not addressed at this meeting.

10. ADJOURNMENT: The meeting adjourned at 1210 hours. The next meeting will be held on 14 May 1999 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas, beginning at 0800 hours. All agenda items are to be submitted to the DoD PEC no later than 14 April 1999.

11. A summary of changes to the BCF and NMOP PDL is attached to these minutes.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chairman	Co-chairman

Summary of BCF Changes

1. Blood glucose test strips: Remove the BCF quantity limitations. MTFs may establish their own quantity limitations.

2. Carbamazepine oral: Remove the "Tegretol brand only" designation

3. Oxybutynin oral: Does not include extended release (Ditropan XL)

4. Phenytoin oral: Remove the "Dilantin brand only" designation

5. Timolol ophthalmic solution: Does not include timolol maleate gel (Timoptic XE)

6. Verapamil oral: Includes only the immediate release dosage forms (Calan, Isoptin, or equivalent) and sustained release dosage forms (Calan SR, Isoptin SR, or equivalent) for which generic equivalent products are available. Verapamil oral does not include other forms of verapamil for which generic equivalent products are not available (such as Verelan, Verelan-PM and Covera-HS).

Summary of NMOP Changes

1. **Added to the NMOP PDL:**
   Abacavir (Ziagen)
   Bisoprolol and hydrochlorothiazide (Ziac)
   Leuprolide (Lupron) subcutaneous injection
   Cetirizine (Zyrtec)
   Fexofenadine and pseudoephedrine (Allegra-D)
   Glimepiride (Amaryl)
   Insulin analog injection (Humalog)
   Lamivudine (Epivir-HBV)
   Leflunomide (Arava)
   Loratidine and pseudoephedrine (Claritin-D 12-Hour and Claritin-D 24-Hour)
   Montelukast (Singulair)
   Norgestimate and ethinyl estradiol (Ortho Tri-Cyclen)
   Tobramycin nebublizer solution (TOBI)
   Urea 40% topical (Carmol-40 and others)

2. **Deleted from the NMOP PDL:**
   Nitroglycerin patches: All brands of nitroglycerin patches other than Nitrodur
   Valacyclovir (Valtrex)

3. **Mapped to other agents on the NMOP PDL:**
   Oxybutynin extended release (Ditropan XL)

Nitroglycerin patches: All brands other than Nitrodur are mapped to Nitrodur
Valacyclovir (Valtrex)

4. **Not on NMOP PDL and not mapped, but prescriptions are filled by NMOP:**
   Papaverine oral
   Urine glucose and urine ketone test strips

5. **Excluded from the NMOP:**
   Celecoxib (Celebrex)
   Etanercept (Enbrel)
   Grepafloxacin dose pack
   Octreotide acetate depot injection (Sandostatin LAR)
   Ofloxacin dose pack
   Quinine
   Valrubicin (Valstar) solution

6. **Other changes/notes:**

   Limit ophthalmic drops for allergic conditions to a maximum of two bottles per month or six bottles per three months.
   Nitrodur is the only brand of nitroglycerin patch listed on the NMOP PDL.

Department of Defense
Pharmacoeconomic Center
1750 Greeley Rd., Bldg. 4011, Rm. 217
Fort Sam Houston, TX 78234-6190

MCCS-GPE 13 November 1998

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with the Office of the Assistant Secretary of Defense (Health Affairs) [OASD(HA)] Policy 98-025, signed 23 March 1998, a meeting of the DoD P&T committee convened at 0800 hours on 13 November 1998, at Fort Sam Houston, TX.

2. MEMBERS PRESENT:

COL William D. Strampel, MC	Co-chairman
COL Errol L. Moran, MS	Co-chairman
COL Rosa Stith, MC	US Army Representative
LTC Judith O'Connor, MC	US Army Representative
Ms. Danielle Doyle, DAC	US Army Representative
CDR Terrance Egland, MC	US Navy Representative
CDR Matt Nutaitis, MC	US Navy Representative
LCDR Denise Graham, MSC	US Navy Representative
LTC William Sykora, MC	US Air Force Representative
LtCol John R. Downs, MC	US Air Force Representative
LtCol (Sel) Greg Russie, BSC	US Air Force Representative
CDR Robert Rist	US Coast Guard Representative
Mr. John Lowe	VA Representative
LTC (P) George Crawford, MS	DMSB Representative
Capt Debra Parrish, BSC	DSCP Representative
Ms. Ray Nan Berry	Foundation Health Representative
Mr. William Hudson	Humana, Inc. Representative
Mr. Gene Lakey	TriWest Representative

3. OTHERS PRESENT:

COL Daniel Remund, MS	US Army
COL Ernest Sutton, M C	US Army

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LCDR Pamela Stewart-Kuhn	US Coast Guard
MAJ Mickey Bellemin, BSC	DSCP
LCDR Mark Richerson, MS	US Navy
Mr. Thomas Kellenberger	Merck-Medco Representative
Mr. Melvin Miller, DAC	US Army
Ms. Carol Scott, DAC	US Army
Mr. Shelby Tanner, SJA	US Army
Dr. Shana Trice, DAC	US Army

4. ISSUES DISCUSSED:

a. COL Strampel opened by stating that this will be his last meeting as co-chair since he is no longer at DoD and is now Chief of Staff for the Assistant Surgeon General of the Army at the Pentagon (1E518). At this time, no replacement has been named, however, COL Strampel stated that he would seek to get a replacement named prior to next meeting.

b. COL Moran introduced new attendees – COL Remund, PEC; MAJ Mickey Bellemi n, who will be Capt Parrish's replacement at DSCP; Mr. Thomas Kellenberger, Merck-Medco (M-M); and LTC (P) George Crawford, Defense Medical Standardization Board (DMSB). COL Moran stated that this would also be his last meeting as a member of the committee. COL Dan Remund, Deputy Director for the PEC will assume COL Moran's role as co-chair.

5. OLD BUSINESS:

a. The committee reviewed the minutes from 14 July meeting. Two changes to be made: (1) On page 5, para 6(e)(i) - change "prenatal" to "prenatal with folic acid 1mg" and change "women" to "female"; and (2) On page 6, para (9) - add weight loss and dental products (Gel-Kam and Peridex). Minutes were approved with these changes.

b. LCDR Graham commented on the last meeting minutes posted on website - Navy facilities have requested a more detailed explanation for why the committee selected/deleted certain products. The committee agreed with this request. (CLOSED)

c. Financial disclosure statements (OGE Form 450) - Mr. Tanner stated that a few members of the committee have not submitted statements. He requested that those named individuals submit such statements as soon as possible. (OPEN)

d. Alternate P&T membership: Coast Guard - LCDR Pamela Stewart-Kuhn; Air Force - LtCol Arnyce Pock and MAJ George Jones; Navy - CDR Mark Brouker and Capt Michael Fredericks; VA - Mr. Ron Moser. Army alternates not yet provided. (OPEN)

e. Fertility drugs - limitations and guidelines : Capt Parrish stated that some women were on fertility drugs for two years without results. As the cost continues to escalate for these drugs, should we continue administering to women who are infertile? COL Strampel stated that

although this is a sensitive issue, a limitation policy should be implemented. The committee recommended that this issue be forwarded to Health Affairs for consideration of establishing a DoD-wide policy. (OPEN)

f. Migraine therapy : This issue was referred to the Clinical Practice Guideline (CPG) group to consider doing a migraine treatment guideline. Their response was that they had no plans to develop a clinical practice guideline for migraine treatment and this would be better served by a PEC dispensing guideline and an educational promotional piece. COL Moran stated that he might not have satisfactorily conveyed the committee's desire to the CPG group. The committee recommended that additional communication be sent to LTC Dolter at MEDCOM, to ask the group to rethink this issue. COL Strampel said that he would also call COL Sid Adkinson on this issue. LtCol (Sel) Russie stated that if this issue is still on the table in January/February, there will be three graduate students coming to the PEC who will need a project to work on. This could be something for them to work on and gather information for guidelines. (OPEN)

g. Policy for Viagra – The policy (HA Policy 98-040) was signed by Dr. Sue Bailey on 6 August 1998. COL Strampel stated that after the policy was released he expressed several concerns about the policy to Health Affairs and sought to write an implementation plan that would clearly outline the intent of the policy. The policy contains ambiguities and questionable provisions such as:

- It appears to open up the special order process at military pharmacies to providers outside the military treatment facility, which was never the intent. The special order process is reserved only for military treatment facility providers.
- Removes Viagra from the National Mail Order Pharmacy (NMOP) formulary which would force many patients to Standard CHAMPUS at a much higher cost to DoD or would possibly cause a switch to Caverject or Muse, also at a higher cost
- Reimbursement of only six tablets per month through Standard CHAMPUS may be unenforceable.

The general counsel agreed that the policy, as written, would cause problems and COL Strampel wrote an implementation policy, which was never sent forward by Health Affairs Clinical. The Air Force has sent out their own implementation guidance and the Army Surgeon General has endorsed the HA policy. COL Moran stated that Viagra prescriptions are currently being filled at the NMOP because of the expected release of an implementation plan that would have authorized doing so. Capt Parrish stated that if Viagra were removed from the NMOP formulary, it would produce thousands of calls per month by Merck-Medco (M-M) to physicians to seek a change to more expensive agents, in which case, most physicians would probably not authorize anyway. In an effort to ensure that NMOP patients meet the HA guidelines, the PEC will develop a one-page guideline sheet which M-M will then fax to the physicians who will sign and certify that all the clinical guidelines have been met and return form within 48 hours. If not returned within that timeframe, M-M will return the prescription and inform the patient that the physician did not fill out the paperwork to have it filled. The committee recommended that COL Strampel go back to Health Affairs/TMA and seek publication of an implementation plan that would eliminate the flaws in the policy as outlined above. (OPEN)

h. NMOP antibiotic dispensing policy : CDR Egland circulated a list of antibiotics that were proposed to be exempt from the 30-day maximum quantity limitation. The committee limited the exemption for three agents (azithromycin, clarithromycin, and ciprofloxacin) to specific indications. Atovaquone and Cephalexin were deleted from the list. The committee approved the list as shown at Enclosure 1. (CLOSED)

i. Early refills - Capt Parrish s tated that M-M has implemented a procedure to handle early refill requests. Refills that are submitted early will be input into their computer, but not be filled for mail out until the due date. As an example, if a refill is due on the 14 th of the month and is sent in on the first, it will be entered and queued for mail out at the appropriate time. New prescriptions will be returned because there is no system in place to queue them for filling. Provisions have also been made for patients who call their prescription in too early. (CLOSED)

j. Oral contraceptives (21/28-day packages) - Capt Parrish stated that DSCP has asked manufacturers to reduce the prices for the 21-tablet packages to be comparable to the 28-tablet prices. Some price reductions have occurred, and some companies have not yet responded. (OPEN)

6. NEW BUSINESS:

a. **Priority Review Drugs - Automatic NMOP and Basic Core Formulary (BCF) Consideration :** None of the agents listed below were added to the BCF. Decisions regarding the NMOP preferred drug list are outlined below:

1) Rebetron® (combination of Rebetol® and Intron-A®) is currently mapped and being filled. **Add to NMOP** because it appears to offer a therapeutic advantage to interferon alone. Also **add to NMOP,** Roferon® and Infergen®.

2) Priftin® (rifapentine) - **Not added to NMOP** at this time. Wait until more usage has occurred before reconsidering. Mapped to rifampin.

3) Thalomid® (thalidomide) – **Exclusion from NMOP** due to restricted distribution requirements and mandatory testing requirements.

4) Preven® - **Exclusion from NMOP** due to time sensitivity of dosing.

5) Arava® (leflunomide) - defer decision pending evidence of usage and place in therapy. Will not be filled at NMOP at this time.

6) Sustiva® (efavirenz) – **Add to NMOP** because of indication.

7) Combivir® (lamivudine/zidovudine) – **Add to NMOP** because no more expensive than total cost of individual drugs. Committee recommended that **all oral retrovirals be added to NMOP.**

8) Xeloda® (capecitabine) – **Add to NMOP** because of indication. Committee recommended that **all oral antineoplastics be added to NMOP.**

9) Evista® (raloxifene) – **Add to NMOP** because of indication.

10) Plavix® (clopidogrel) – **Add to NMOP** because of indication and advantages to ticlopidine in aspects of dosing, monitoring requirements, and incidence of adverse effects..

11) Sulfamylon® (mafenide acetate powder) for 5% topical solution. **Not added to NMOP.** Cream is already on the NMOP. The solution has to be freshly prepared, so it is not a suitable dosage form for dispensing via the NMOP.

12) Detrol® (tolterodine) - Request from Naval Medical Center in Portsmouth to add to NMOP. Currently mapped to oxybutynin with a 20% success rate of switching. Currently, 370 patients are receiving 1mg or 2mg tablets through the NMOP. Although tolterodine has a slightly better side effect profile than oxybutynin, the committee voted to **not add to NMOP** because it is not more effective than oxybutynin and costs over four times as much.

b. **Other NMOP Issues:**

1) **Add to NMOP** – Rondec® oral drops because of listing on BCF.

2) **Add to NMOP** – Inhaler Spacers because of listing on BCF.

3) **Delete from NMOP** – Herplex® ophthalmic drops because no longer manufactured.

4) Mapping of agents by the PEC – drugs that have been mapped are: new angiotensin II receptor blocker candesartan (Atacand®) mapped to losartan, valsartan; new migraine agent rizatriptan (Maxalt® & Maxalt MLT®) mapped to sumatriptan; new SSRI citalopram (Celexa®) mapped to fluoxetine, sertraline, paroxetine; new low estrogen oral contraceptive Levlite® mapped to other oral contraceptives; mephobarbital (Mebaral®) mapped to phenobarbital; and mephenytoin (Mesantoin®) and ethotoin (Peganone®) mapped to phenytoin.

c. **BCF Issues:**

1) Non-steroidal ophthalmic agents – Fort Leavenworth requested a review of this class of drugs. Current BCF selection is flurbiprofen (Ocufen®), which lacks a primary care indication. Ketorolac (Acular®) would appear to be a more logical BCF selection because of its primary indication, however, it is more expensive than flurbiprofen. COL Moran also questioned if one is even needed for the BCF. It was suggested that local commands make their own selection. Mr. Lakey questioned the impact on the Managed Care Support contractors or inconvenience to patients. COL Strampel commented that removal of a drug from the BCF does not necessarily effect an MTF formulary because most facilities will more than likely keep an agent in this class on their local formulary. The committee removed Ocufen® from the BCF because it does not have a primary care indication that is necessary for inclusion on the BCF. The committee also did not recommend any other such agent for the BCF, preferring to let MTFs make their own choice.

2) Budesonide (Pulmicort®) and fluticasone (Flovent®) Oral Inhalers (see Enclosure 2): The committee approved the recommendation that budesonide and fluticasone oral inhalers be removed from the BCF for the reasons given in the enclosure. CDR Egland opposed removal from the BCF because his facility advocates that it is more cost effective in a subset of patients. The remaining committee members agreed that it is possible that these agents may be more cost effective for certain patients requiring high doses. However, there is insufficient evidence in the literature to strongly support this claim, and the committee does not want to mandate that facilities have a drug available at 3 to 8 times the cost of equally effective agents. Also, this decision does not prohibit individual MTFs from including these agents on their local formulary. These agents will remain on the NMOP.

3) Consider removal of specific brand designation (i.e., Coumadin® brand only) from the BCF because an AB rated generic agent is available. The primary reason the BCF listed

"Coumadin® brand (Dupont) only" is historical in nature. Back in the days of the depot system, DMSB had designated a few items as "sole source", meaning that only a designated brand could be purchased. At some point in time, Dupont brand warfarin was added as a "sole source" item. This listing carried over to the TriService Formulary (the predecessor to the BCF), then to the BCF. Also, there were not AB-rated warfarin products at that time. The first question is whether it is appropriate to have the brand name only designation on the BCF? Clinical evidence, from crossover studies, shows no difference in brand name vs. generic warfarin. Both are equally safe and efficacious according to the FDA. One initial difference is that Dupont-Merck, the maker of Coumadin®, came out with 3mg and 6mg strengths, which Barr, the maker of an AB-rated generic warfarin, did not have. However, Barr now does provide 3mg and 6mg strengths. Barr also does not currently provide the drug in unit dose packaging. Barr is anticipating providing unit dose packaging next spring. The generic tablets provided by Barr are scored, imprinted with the dosage strength, and are provided in the same color-strength combinations as the Dupont-Merck product. After discussion, the committee unanimously approved the removal of specific brand designation [i.e., Coumadin® brand (Dupont) only] from the BCF. The product will be listed on the BCF as "Warfarin oral". With this change, MTFs are now free to make their own choice as to which warfarin product is provided at their facility. The second question asked was should DoD contract for a sole source warfarin product in order to provide uniformity of product availability throughout DoD and, at the same time, generate cost savings? The committee agreed that a contract for a sole source warfarin product for DoD, either unilaterally or jointly with the VA, should be sought. COL Remund suggested that the committee make an interim special designation for dispensing warfarin through the NMOP to avoid potentially switching patients from the brand name to the generic and back to the brand name (depending on which agent is selected for the contract). The special designation would be that switching NMOP patients to generic warfarin would be held in abeyance until the contracting issue is completed. No calls will be made on prescriptions for Coumadin® , they will be filled as written. If a prescription comes in as "warfarin" or "substitution allowed", then the prescription can be filled with generic warfarin. The committee agreed. (CLOSED)

4) Long-acting nifedipine: Currently, the BCF states that all facilities must have a long-acting nifedipine on their formulary, the choices being either Adalat CC® or Procardia XL®. An MTF may have both on their formulary , however, they are not required to have both. COL Remund suggested that the PEC and DSCP go out for a blanket purchase agreement to identify the single form of nifedipine extended release that would be placed on the BCF without the closing the class. This would allow flexibility for MTFs who want both drugs and it would also achieve uniformity and possibly lower prices. Currently, the DAPA prices for Adalat CC® are $0.46 per tablet for all strengths (30mg, 60mg, & 90mg). DAPA per tablet prices for Procardia XL® are $0.65 for 30mg, $1.18 for 60mg, & $1.20 for 90mg. Since the VA has selected Adalat CC® as their preferred long-acting nifedipine and current prices favor Adalat CC®, COL Strampel recommended that the following be listed on the BCF: "Long-acting nifedipine (Adalat CC®) – class remains open. MTFs must have Adalat CC® on their formulary, but may choose to also have Procardia XL®". Again, this will help to establish uniformity across DoD, yet, allow MTFs to also add Procardia XL® if they so desire. The committee agreed. The committee also agreed that only Adalat CC® should be listed on the NMOP. Procardia XL® will be removed from the NMOP Preferred Drug List. (CLOSED)

5) Angiotensin II Receptors - should one be included on the BCF? The committee does not support adding such an agent to the BCF because most patients can be successfully treated with an ACE inhibitor. Should DSCP seek BPAs with the manufacturers in an effort to obtain lower prices? The committee supported this strategy , however, one will not be placed on the BCF. (OPEN)

d. **Contracting Issues:**

1) Non-sedating antihistamines – seek price reductions through BPAs, but not for the purpose of putting one on the BCF. Motion passed. (OPEN)

2) Selective Serotonin Reuptake Inhibitors (SSRIs) – COL Sutton stated that the proposed strategy is to select one SSRI for placement on the BCF and NMOP. The SSRI class would remain open on the BCF and the NMOP. This strategy would ensure uniform availability of one SSRI throughout DoD. Local P&T committees could add additional SSRIs to their formularies as necessary to meet the clinical needs of patients and the preferences of MTF providers. The committee approved the proposed contracting strategy and five of the six proposed evaluation factors as presented by Mr. Miller. These evaluation factors may be contract sensitive, therefore, specific details are not provided in these minutes. (OPEN)

3) Proton Pump Inhibitors (PPIs) – COL Sutton stated that the proposed strategy is to seek a sole source contract through DPSC to select one PPI, either omeprazole (Prilosec®) or lansoprazole (Prevacid®), for the BCF and NMOP. The PPI class would be closed. This means that the selected agent will be the only PPI that will be dispensed through the NMOP and at MTFs. MTFs would still be able to utilize a local special order process for patients not successfully treated with the selected agent. Managed Care Support contractors would use the prior authorization process for prescriptions that are for the agent not selected. The NMOP contract does not allow for the prior authorization process, therefore, only the selected agent will be dispensed through the NMOP. The committee approved the strategy. (OPEN)

4) Glucose Test Strips – LtCol (Sel) Russie stated that the proposed strategy is to seek a sole source contract through DPSC to select one glucose test strip for the BCF and NMOP, with the class being closed. Five companies have made pre-solicitation presentations. The committee approved the proposed contracting strategy and the evaluation factors as presented by LtCol (Sel) Russie. These evaluation factors may be contract sensitive, therefore, specific details are not provided in these minutes. Target date for issuing the solicitation is January/February timeframe. (OPEN)

5) Fluoroquinolones – Does the committee think it's reasonable to have a fluoroquinolone on the BCF? One concern raised by LtCol (Sel) Russie was do we really want to mandate a fluoroquinolone on small facilities or clinics? The committee members agreed that every facility should have a fluoroquinolone on their formulary. A notation will be place on the BCF that will indicate that each facility must have a fluoroquinolone on their formulary. A specific fluoroquinolone will not be selected unless a clear choice can be made due to voluntary price reductions. Until a BCF selection is made, individual facilities will make their own choice as to which fluoroquinolone is carried on their formulary. (OPEN)

e. Other Issues:

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1) Palivizumab (Synagis®) - Do we need prescribing guidelines for this agent? One issue is that some MTFs are/were sending patients downtown to obtain the drug and brought back to the hospital for administration. TriWest has had numerous communications with TMA to get this issue resolved, without success. COL Strampel will discuss this issue with the medical director of TMA. COL Strampel stated that it should be emphasized that if the hospital has responsibility for the primary care of the patient, they should be taking care of them and not sending them out. If the hospital does not have the capability for such treatment, which is unlikely, then, they should terminate their care and turn the patient over to the contractor. If the hospital is already providing the care, it is their responsibility to obtain the drug for the patient. Dr. Egland provided the committee with criteria for use of Synagis® and Respigam® that are being used at Naval Medical Center, Portsmouth, VA. LtCol (Sel) Russie recommended that these guidelines be attached to the minutes of this meeting to serve as a guide for developing local guidelines. The committee approved this recommendation (see Enclosure 3). (CLOSED)

2) Status of statins contract - COL Remund stated that DSCP issued the statin solicitation on 23 Oct 98. Offers are due on 23 Nov 98. The solicitation was issued without a final review by the PEC. DSCP is working on an amendment to correct various errors and modify certain clauses in the solicitation. DSCP may decide to extend the due date for offers. COL Remund reiterated the strategy that was approved at the last P&T meeting – the class will be closed and a minimum of one, maximum of two statins will be selected for the BCF and NMOP. Either atorvastatin or simvastatin will be selected in order to meet the needs of patients requiring large reductions in LDL-C. A contract will be established for a second statin if the addition of the second statin to the BCF and NMOP is predicted to be more cost-efficacious than atorvastatin or simvastatin alone. (OPEN)

3) Request that quantity limitations which are in effect at the NMOP be equally applied to prescriptions filled by the TRICARE contractors. The committee position was that an appeal be made to TMA to allow this. COL Strampel stated that this was an issue going back to HA to ask if they will write a policy to do this as a first step. (OPEN)

4) COL Strampel raised the issue of flu shots for all the children in the world. Will this raise any problems or impact us? May become a bigger issue by next year. Put on the agenda for next meeting. (OPEN)

5) Capt Parrish raised one issue of a letter she received from TMA concerning non FDA-approved indications for some odd things such as Nizoral® for prostate cancer, Clomid® for men, tamoxifen for brain cancer, etc. COL Moran stated that current rules allow for filling of prescriptions for off-label use if there is literature substantiating such use. TMA said they would pay for it under standard CHAMPUS although CHAMPUS does not set forth who conducts the medical review and who makes the ultimate decision. The rules aren't very clear. The decision for the committee may be that because of the limited number of patients in this situation it would be beyond the scope of the NMOP to deal with. Therefore, prescriptions for off-label indications would not be filled by the NMOP, on a routine basis. (CLOSED)

7. ADJOURNMENT:

MCCS-GPE
SUBJECT: Minutes of the Department of Defense Pharmacy & Therapeutics Committee Meeting, 13 November 1998

The meeting adjourned at 1215 hours. Location and date of next meeting has been set for 5 February 1999, 0800 hrs, at Health Affairs in Skyline Five. This will coincide with the TRICARE meeting, 1-5 Feb, in Washington, DC.

Enclosures

ERROL L. MORAN
COL, MS
Co-chairman

WILLIAM D. STRAMPEL
COL, MC
Co-chairman

MCCS-GPE
SUBJECT: Minutes of the Department of Defense Pharmacy & Therapeutics Committee Meeting, 13 November 1998

Summary of BCF Changes

1. **Additions:**
   Nifedipine long-acting (Adalat CC®) (see pg 6-7)
2. **Deletions:**
   Budesonide (Pulmicort®) (see pg 5-6)
   Flurbiprofen (Ocufen®) (see pg 5)
   Fluticasone (Flovent®) (see pg 5-6)
   Nifedipine long-acting (Procardia XL®) (see pg 6-7)
3. **Other changes/notes:**
   Removal of "Coumadin® brand (Dupont) only" notation for Warfarin (see pg 6)
   Removal of notation that MTFs must have one long-acting nifedipine. The long-acting nifedipine of choice is Adalat CC® (see pg 6-7)

Summary of NMOP Changes

1. **Additions:**
   Combivir® (see pg 4)
   Evista® (see pg 4)
   Infergen® (see pg 4)
   Inhaler spacers (see pg 5)
   Plavix® (see pg 5)
   Rebetron® (see pg 4)
   Roferon® (see pg 4)
   Rondec oral drops (see pg 5)
   Sustiva® (see pg 4)
   Xeloda® (see pg 4)
2. **Deletions:**
   Herplex® ophthalmic drops (see pg 5)
   Procardia XL® (see pg 6-7)
3. **Exclusions:**
   Preven® (see pg 4)
   Thalidomide (Thalomid®) (see pg 4)
4. **Other changes/notes:**
   Approved list of antibiotics exempt from 30-day maximum quantity limitation (see pg 4)
   Merck-Medco implemented procedure for handling early refill requests (see pg 4)
   In future, all oral antineoplastics and oral retrovirals will be added automatically (see pg 4)
   Some price reductions obtained on 21-day oral contraceptives (see pg 4)
   Removal of Coumadin® brand only – patients not to be switched to generic, yet (see pg 6)

8:00 ANTI-INFECTIVE AGENTS EXEMPT FROM THE NMOP 30 DAY TREATMENT LIMIT

AHFS Classification	Anti-Infective Agent	FDA Indication	Non-FDA Indication	Comments
8:04 Amebicides (none – tx <20 days)				
8:08 Anthelmintics (none – tx is 30 days or less)				
8:12 Antibiotics				
8:12.04 Antifungal				
8:12.04 (addition)	Fluconazole (Diflucan®)	Cryptococcal, thrush prophylaxis & coccidiomycoci		
8:12.04	Flucytosine (Ancobon®)	Candida or Cryptococcus septicemias & UTI	Chromomycosis	
8:12.04	Griseofulvin (Fulvicin®, etc)	Ringworm infections		
8:12.04	Itraconazole (Sporanox®)	Blastomycosis, Histoplasmosis, Aspergillosis, Onychomycosis	Dermatophytoses, Pityriasis versicolor, Sebopsoriasis, Candidiasis	
8:12.04	Ketoconazole (Nizoral®)	Systemic funal infections	Onychomycosis, pityriasis versicolor, tinea pedis, corporis and cruuris, tinea capitis and vaginal candidiasis; advanced prostate ca; cushing's syndrome	
8:12.04	Nystatin (Mycostatin®, Nilstat®)	Candidiasis		
8:12.04 (addition)	Terbinafine (Lamisil®)	Onchomycosis		
8:12.06 Cephalosporins (deletion)				
8:12.06 (deletion)	Cephalexin (Kelfex®)		UTI Prophylaxis and osteomyelitis	
8:12.12 Macrolides				
8:12.12 (addition)	Erythromycin	Acne		
8:12.12 (addition)	Azithromycin	Mycobacterium avium Complex		**Over 30 days only for listed indication(s)**
8:12.12 (addition)	Clarithromycin	MAC		**Over 30 days only for listed indication(s)**
8:12.16 Penicillins				
8:12.16 (addition)	Penicillin V K or Penicillin G	Prophylaxis of Pneumococcal Infections and recurrent rheumatic fever	SS dx	
8:12.16 (addition)	Amoxicillin (Amoxil®)	Chronic UTI tx.		

AHFS Classification	Anti-Infective Agent	FDA Indication	Non-FDA Indication	Comments
8:12.24 Tetracyclines				
8:12.24 (addition)	Doxycycline (Vibramycin®)	Chemoprophylaxis of malaria		
8:12.24	Minocycline (Minocin®)	Inflammatory acne, Nocardiosis		
8:12.24	Tetracycline (Sumycin®)	Inflammatory Acne, H. Pylori, actinomycosis		
8:12.28 Miscellanous				
8:12.28 (addition)	Clindamycin (Cleocin®)	Toxoplasmosis, acne vulgaris		
8:16 Antituberculosis Agents				
8:16 (addition)	P-Aminosalicylic Acid (Sodium P.A.S®)	Retreatment of TB		
8:16 (addition)	Cycloserine (Seromycin®)	Active pulmonary & extrapulmonary TB		
8:16	Ethambutol (Myambutol®)	Primary agent in tx of TB		
8:16	Ethionamide (Trecator-SC®)	Treatment of TB when first line fails		
8:16	Isoniazid	Primary tx of TB		
8:16	Rifamate® - 150 mg INH with 300 mg Rifampin	Primary tx of TB		
8:16	Rifater® - 50 mg INH with Pyrazinamide 300 mg and Rifampin 120 mg	Primary tx of TB		
8:16	Pyrazinamide	Primary tx of TB		
8:16	Ribabutim (Mycobutin®)	Prevention of disseminated MAC		
8:16	Rifampin (Rifadin®)	Primary tx of TB		
8:18 Antivials				
8:18	Acyclovir (Zovirax®)	Chronic suppresssive tx of genital herpes		
8:18	Amantadine (Symmetrel®)	Influenza A Chemoprophylaxis		
8:18 (addition)	Famciclovir (Famvir®)	Suppression of genital herpes		
8:18	Ganciclovir (Cytovene®)	Prevention of CMV in HIV pts		
8:18 (addition)	Rimantadine	Prophylaxis of		

	(Flumadine®)	various strains of influenza A		

AHFS Classification	Anti-Infective Agent	FDA Indication	Non-FDA Indication	Comments
8:18.08 Antiretroviral Agents (all agents in class such as those listed here as new additions to class)				
8:18.08	Delaviridine Mesylate (Rescriptor®)	HIV Infection		
8:18.08	Didanosine (Videx®)	HIV Infection		
8:18.08	Indinavir (Crixivan®)	HIV Infection		
8:18.08	Lamivudine (Epivir®)	HIV Infection		
8:18.08 (addition)	Lamivudine/ Zidovudine (Combivir®)	HIV Infection		
8:18.08	Nelfinavir Mesylate (Viracept®)	HIV Infection		
8:18.08	Nevirapine (Viramune®)	HIV Infection		
8:18.08	Ritonavir (Novir®)	HIV Infection		
8:18.08	Saquinavir (Invirase®)	HIV Infection		
8:18.08	Stavudine (Zerit®)	HIV Infection		
8:18.08	Zalcitabine (Hivid®)	HIV Infection		
8:18.08	Zidovudine (Retrovir®)	HIV Infection		
8:20 Antimalarial Agents				
8:20	Chloroquine (Aralen®)	Malaria prophylaxis		
8:20	Hydroxychloroquine (Plaquenil®)	Malaria, lupus erythematous, rheumatoid arthiritis		
8:20	Mefloquine (Lariam®)	Malaria prophylaxis		
8:20	Pyrimethamine (Daraprim®)	Chemoprophylaxis of malaria, Toxoplasmosis		
8:20	Pyrimethamine/ Sulfadiazine (Fansidar®)	Malaria, toxoplasmosis		
8:20 (addition)	Doxycycline	Malaria Prophylaxis		
8:22 Quinolones				
8:22 (addition)	Ciprofloxacin (Cipro®)	Osteomeylitis, prostatitis, Mycobacterial Inf		**Over 30 days only for listed indication(s)**
8:24 Sulfonamides				
8:24 (addition)	Sulfadiazine	Toxoplasmosis in HIV , Nocardiosis, Prophylaxis of		

		Recurrent Rheumatic fever		
8:24	Sulfasalazine (Azulfidine®)	Ulcerative colitis		

AHFS Classification	Anti-Infective Agent	FDA Indication	Non-FDA Indication	Comments
8:26 Sulfones				
8:26	Dapsone	Leprosy, Dermatitis Herpetiformis, Malaria, PCP		
8:36 Urinary Anti- Infectives				
8:36 (addition)	Methenamine (Hiprex®, Urex®)	Prophylaxis of recurrent UTI		
8:36 (addition)	Nitrofurantoin (Macrodantin®)	Prophylaxis of recurrent UTI		
8:36 (addition)	Trimethoprim (Trimpex®)	Suppression of recurrent UTI, PCP		
8:40 Miscellaneous Anti- Infectives				
8:40 (deletion)	Atovaquone (Mepron®)	Pneumocystits carinii		750 mg bid for 21 days therefore <30 days.
8:40	Clofazimine (Lamprene®)	Leprosy	Tx of MAC, mycobatcterial infections	
8:40 (addition)	Co-trimoxazole	PCP prophylaxis, Nocardia, pneumonic plaque,, toxoplasmosis prophylaxis		

Budesonide and Fluticasone

1. Objective

a. Should Pulmicort Turbuhaler® (budesonide) and Flovent® (fluticasone) be retained on the Basic Core Formulary?

2. Cost Comparison Chart

Drug	Equivalent Puffs	Cost of Equivalent Puffs
Triamcinolone	4	$0.12
Flunisolide	4	$0.12
Beclomethasone 42 mcg	2	$0.04
Beclomethasone 84 mcg	1	$0.04
Fluticasone 44 mcg	4	$0.44
Fluticasone 110 mcg	2	$0.36
Fluticasone 220 mcg	1	$0.35
Budesonide 100 mcg	1	$0.33

3. Areas Where Evidence Is Sufficient

a. Clinical trials suggest that pulmicort and fluticasone are equally efficacious compared to other oral inhaled corticosteroids when used in equipotent doses.

b. Clinical trials suggest that use of higher potency corticosteroid inhalers results in patients being maintained on fewer puffs per day, possibly enhancing compliance.

c. Some patients may find benefit in using an inhaler that delivers an effective dose with fewer puffs per day.

d. Some patients may find budesonide's dry powder inhaler/delivery device easier to use than inhalers requiring coordination of a spacer device.

4. Areas Where Evidence Is Lacking

a. The PEC's selection of fluticasone and budesonide for inclusion on the BCF was based on an analysis of the effect of steroid inhaler usage on total costs (i.e. admissions, emergency department visits, lost productivity). However, this analysis may have overestimated the effect of multi-puff administration on regimen compliance.

b. There is no evidence in the literature that directly correlates the prescribed number of puffs per administration with adherence to the prescribed regimen.

c. There is no evidence in the literature that the benefits of fluticasone and budesonide (fewer puffs per day, increased compliance, and ease of use) directly produce a quantifiable, statistically significant difference in clinical outcomes (admissions, E.D. visits, symptom free days) of asthma care.

4. Recommendation:

The DOD PEC recommends that Pulmicort (budesonide) and Flovent (fluticasone) be removed from the BCF for the following reasons:

1. Lack of quantifiable evidence in the literature that the benefits of these drugs directly influence the clinical outcomes of asthma significantly more than their lower potency comparator drugs.

2. Possibility that the PEC's earlier analysis of asthma corticosteroid therapy may have overestimated the effect of potentially improved compliance on the overall cost of asthma therapy.

Eugene Moore, PharmD
DOD Pharmacoeconomic Center

Criteria for Use of Synagis® and Respigam® To Select Infant Patients*

1. For use with the approval of a staff neonatologist, pediatric pulmonologist, or pediatric cardiologist between the months of November and April.

2. Infants born at or less than 28 weeks gestational age, with or without the diagnosis of Chronic Lung Disease (CLD), and less than 12 months corrected age.

3. Infants born between 29 and up to 32 weeks gestational age with the diagnosis of CLD and less than 12 months corrected age.

4. Infants born between 29 and up to 32 weeks gestational age without the diagnosis of CLD and less than 6 months of corrected age.

5. Premature infants born at greater than 32 weeks gestation, discharged between November and March, will be considered on a case by case basis. Consideration will be given to severity of lung disease, need for supplemental oxygen and pulmonary medications.

6. Infants in the NICU at highest risk for severe RSV morbidity, potentially exposed to an index case of RSV in the NICU.

7. Patients with a diagnosis of CLD and less than two years of age who have received oxygen or medications (steroids, diuretics) for CLD within the past 6 months.

8. Infants with congenital heart disease will be considered on a case by case basis by a neonatologist or pediatric cardiologist.

9. Infants with cystic fibrosis, other forms of chronic lung disease, or pulmonary hypoplasia, will be considered on a case by case basis by a neonatologist or pediatric pulmonologist.

***** These criteria were prepared for use at Naval Medical Center, Portsmouth, VA, and is intended as a guide for use by medical treatment facilities within DoD

Department of Defense

Pharmacoeconomic Center
1750 Greeley Rd., Bldg. 4011, Rm. 217
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MCCS-GPE 14 July 1998

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee Meeting

1. In accordance with the Office of the Assistant Secretary of Defense (Health Affairs) [OASD(HA)] Policy 98-025, signed 23 March 1998, a meeting of the DoD P&T committee convened on 13-14 July 1998, at Fort Sam Houston, TX.

2. MEMBERS PRESENT:

COL William D. Strampel, MC	Co-chairman
COL Errol L. Moran, MS	Co-chairman
COL Rosa Stith, MC	US Army Representative
LTC Judith O'Connor, MC	US Army Representative
Ms. Danielle Doyle, DAC	US Army Representative
CDR Terrance Egland, MC	US Navy Representative
CDR Matt Nutaitis, MC	US Navy Representative
LCDR Denise Graham, MSC	US Navy Representative
LTC William Sykora, MC	US Air Force Representative
LtCol John R. Downs, MC	US Air Force Representative
MAJ Greg Russie, BSC	US Air Force Representative
CDR Robert Rist	US Coast Guard Representative
Mr. John Lowe	VA Representative
LtCol Wayne Cheatum, BSC	DMSB Representative
Capt Debra Parrish, BSC	DSCP Representative
Ms. Ray Nan Berry	Foundation Health Representative
Mr. William Hudson	Humana, Inc. Representative
Mr. Gene Lakey	TriWest Representative

3. OTHERS PRESENT:

CAPT Chuck Bruner	USCG
COL Patricia Hobbs, BSC	USAF

COL James Normark, BSC	USAF
COL Ernest Sutton, MC	USA
COL Roger F. Williams, MS	USA
Mr. Shelby Tanner, SJA	USA

4. ISSUES DISCUSSED:

a. P&T Committee members introduced themselves and gave a background review of their experience. COL Moran introduced the members of the DoD Pharmacy Board of Directors, managed care support contractors, and other attendees.

b. MAJ Russie gave a presentation on the global perspective of formulary management and an overview of the drug distribution systems within DoD.

c. COL Moran provided the committee with a background review of how and why this committee was formed and the role of the PEC.

d. Mr. Shelby Tanner explained the need for each member to fill out an OGE 450 form (Financial Disclosure Statement). Each member is required to fax a copy of this form to the PEC by next meeting date.

e. Selection of physician co-chair: COL Strampel, as a representative of TRICARE Management Activity, will serve as co-chair.

f. Meeting schedules, locations and meeting process: The next P&T committee meeting will be held 13 November 1998, in conjunction with the AMSUS meeting, in San Antonio, TX. Exact location to be determined. Subsequent meetings will be scheduled at each future meeting. The committee will request through the appropriate commands that an alternate representative be nominated for each member in the event the primary member is unable to make a meeting. The uniform for meetings will be casual civilian attire. Discussions will be limited to agenda items, unless there is a pressing issue. Submissions of topics for inclusion on the agenda should be submitted as soon as possible. The deadline for items to be included on the agenda is 30 days prior to meeting.

g. Policies/procedures regarding communication and interaction between pharmaceutical representatives and DoD P&T committee members: All communication, dealing with P&T issues, are to be routed through the PEC. COL Moran will assign a PEC staff member (non-P&T member) as a liaison. Individual members will determine to what extent they will interact with pharmaceutical representatives at their facility.

h. CDR Egland questioned who was the approval authority for P&T issues and meeting minutes. COL Moran responded that, as per the policy that established this committee, the P&T committee is the final approving authority for any and all changes to the BCF/NMOP and the meeting minutes, which will be posted to the PEC web page.

i. Policies/procedures for including/excluding/deleting products on the BCF/NMOP and Special Purchase Request Data Sheet: All Medical Treatment Facilities (MTFs) may submit requests for changes to the DoD P&T committee. Such requests must be recommended by the MTF P&T committee and approved by the MTF commander and must provide all information as required by Appendix A of the policy that established the DoD P&T committee. All MTFs will be notified of this requirement. The special purchase data sheet (Appendix B of the DoD P&T policy) will not come into effect until therapeutic classes are closed. Patient care will be the main focus as opposed to saving money.

j. Mechanism for interim changes: When an issue arises that requires timely action, COL Moran will call together a subgroup of the membership to develop a decision, which will then be communicated to all members for a consensus. This process will be accomplished within 48 hours. Such actions will be formally approved at the next scheduled meeting. In order to facilitate this process, COL Moran requested that each member inform him of all leaves or absences.

k. Treatment guidelines development: COL Moran informed the membership that DoD and VA are working together to develop treatment guidelines for specific diseases. The current joint effort includes: Tier 1: smoking cessation, hypertension, and lower back pain; Tier 2: reactive airway diseases, hyperlipidemia, AMI, and diabetes; Tier 3: depression/suicide prevention. A PEC member is involved in each of the workgroups. Decisions by these workgroups may affect decisions this P&T committee makes and vice versa.

l. Contracting Issues:

(1) Joint ventures with the VA:

(a) A Federal Pharmacy Executive Steering Committee (FPESC) was formed which will meet in August 1998 to identify classes of drugs suitable for joint contracting efforts. Both co-chairs of the DoD P&T committee are members of the FPESC.

(b) There currently are several contracting initiatives ongoing. These include: long-acting diltiazem, generic albuterol inhaler, generic cimetidine and ranitidine, and the SSRI class of drugs.

(2) Strategies and technical evaluation factors for product selection: DoD very much wanted to join with the VA in contracting for one or more HMG-CoA reductase inhibitors (statins), however, the VA unilaterally decided to continue with their current contract for lovastatin and simvastatin. Therefore, DoD (PEC and the Board of Pharmacy) decided to pursue a separate contract. COL Moran explained the proposed contracting strategy. He also explained the technical evaluation factors that the PEC is proposing for selecting the agent(s). The committee approved, unanimously, both the strategy and the technical evaluation factors.

(3) Categories for future contracting: COL Moran explained that efforts to pursue contracts are generally based on high-dollar, high-volume agents or drug classes. As such, the following list of drugs/classes were considered for contracting initiatives: Proton pump inhibitors, ACE inhibitors, long-acting nifedipine, and glucose test strips. The committee approved pursuing contracting initiatives for these, whether jointly with the VA, or unilaterally through the Defense Supply Center Philadelphia (DSCP). The decision to pursue joint contracts will be made by the

FPESC. Once efforts are underway, the interim decision process will be utilized for decisions on contracting strategies and use of technical evaluation factors.

m. BCF issues to be addressed:

(1) Deletion of Idoxuridine Ophthalmic Soln - no longer available: Committee concurred. In the future, all discontinued drugs will be automatically removed from the BCF and the committee will be notified at the next scheduled meeting. (CLOSED)

(2) Request from Madigan Army Medical Center (MAMC) to remove blood glucose test strips from BCF: The committee unanimously agreed that test strips should remain on the BCF because of the need to provide a uniform benefit across the Military Health System. COL Moran will prepare and send a response letter to MAMC, explaining the committee's decision. (CLOSED)

(3) Other issues: Mr. Bill Hudson, Humana, asked "When a class is closed, how long is it locked out for?" COL Moran responded that drug classes would only be closed through the issuance of a contract and that most contracts are for five years with annual renewal options. (CLOSED)

n. NMOP Issues to be addressed:

(1) Capt Parrish provided the committee with a brief history and summary of the NMOP program. She explained to the committee that DSCP is utilizing the formulary, prepared by the PEC, as a preferred agent list. If a prescription comes in for something that is not on the list, the mail order contractor, Merck-Medco (M-M), will call the physician and ask if the item can be switched to something that is on the list. If the prescriber does not want to change, then M-M will fill the prescription as written. (CLOSED)

(2) Combination products where both ingredients are currently on the preferred drug list: Since the patient would be required to pay two co-pays and the government two dispensing fees, the committee decided that the majority of such combination products should be added to the NMOP formulary. However, if the cost/benefit ratio comes into question (i.e., the price of the combination product is more than the cost of the two individual ingredients and the two dispensing fees), then the issue will be brought before the committee. (CLOSED)

(3) Dispense as written: The contractor fills between 2,000 and 3,000 such prescriptions per month. The Statement of Work (SOW) states that mandatory generic substitution will be utilized, unless the doctor justifies that a brand name product is necessary. Capt Parrish reviews all of these claims and there are many justifications that are questionable. She suggested that one way to handle such prescriptions is for M-M to FAX the prescriber a standardized form to justify the use of a brand name. Prescriber would be required to return the completed form prior to filling the prescription. If the doctor refuses to fill out the form, the medication will not be dispensed as written. The committee approved this recommendation with a few changes to include the date the physician reported the adverse reaction to the FDA. The following products will be dispensed as written: Birth control pills, carbamazepam (Tegretol®), digoxin (Lanoxin®), phenytoin sodium (Dilantin®), and warfarin sodium (Coumadin®). Currently, thyroids are also dispensed as written. That is to say, Synthroid filled with Synthroid, Levothroid with Levothroid, etc. (CLOSED)

(4) Coverage of antibiotics: Current policy is a maximum of a 21-day supply, if not on the exempt list (approximately 38 anti-infectives – includes antivirals, antifungals, & antibiotics).

The committee agreed that antibiotics should be filled through the NMOP, but only up to a 30-day supply, unless included on the exempt list. If a prescription is received for a greater than 30-day supply and drug is not on the exempt list, but has a definitive FDA approved diagnosis, the prescription will be filled for the greater amount. If the same occurs, but no diagnosis is given, the prescription will be filled for a 30 day supply. The explanation of benefits will direct them to member services to determine how to facilitate the 90 day supply. When a diagnosis is provided, M-M will fill the balance of the prescription and the additional co-pay for the patient will be waived. However, the government will incur the additional dispensing fee expense. CDR Egland will lead a subgroup (CDR Graham, Capt Parrish, and Ms. Doyle) to review the exempt list for potential changes. Capt Parrish will provide him with a printout of questionable greater than 30-day prescriptions. (OPEN)

(5) Coverage of vitamins: The committee decided that no changes need to be made.

(6) Review of product limitations in NMOP: The committee decided the following:

(a) Fertility Drugs – remain as a maximum of 30-day supply. PEC to review and provide recommendation to the committee. (OPEN)

(b) Diabetic Test Strips – change to a maximum of 400 strips per 90 days for insulin dependent diabetics and 100 strips per 90 days for non-insulin dependent diabetics. Same limitations for BCF. (CLOSED)

(c) Insulin syringes – remain at a maximum of 300 per 90 days. Same limitation for BCF. (CLOSED)

(d) Anti-emetics – remain at 15 tablets/30 days to max of 45 tablets/90 days. (CLOSED)

(e) Impotence – Viagra® to remain at maximum of 6 tablets per 30 days. Caverject® and Muse® changed to maximum of 6 per 30 days. (CLOSED)

(f) Migraine therapy – Imitrex® to remain as a maximum of 48 tablets of 25mg, 24 tablets of 50mg, and 8 injections per 30 days. New agents, such as the nasal product will default to the M-M clinical max. The committee recommends that the DoD/VA Practice Guideline Group consider addressing the need for guidelines for treating this condition. A letter will be sent to the group. (OPEN)

(g) High Dollar Pharmaceuticals – to remain unchanged; list includes a 30-day supply for myeloid stimulants, Interferon Alpha, Interferon Gamma, Erythroid stimulants, Sandostatin®, anti-hemophilic factors, and factor IX preps; and includes a 90-day supply for interferon beta, growth hormones, and Copaxone®. (CLOSED)

(h) Retin-A® – to remain unchanged; only to patients up to age 35. (CLOSED)

(i) Prenatal Vitamins – to remain unchanged; only to women up to age 45. Same limitations for BCF. (CLOSED)

COL Hobbs suggested that any future quantity limitations and preferred agent status that applies to the NMOP should also be the same for the retail network. The committee agreed, however, such changes will probably have to be approved by TMA-West.

(7) New FDA approved products – "mapping" to preferred agent list: "Mapping" refers to the process where newly marketed pharmaceuticals, that are not included on the NMOP, are matched against a drug or class of drugs that are on the NMOP. This will allow M-M to call prescribers of these newly marketed pharmaceuticals and request a change. Capt Parrish stated that until a newly marketed agent is "mapped", M-M would not be able to fill any prescriptions

for the agent. The committee's decision was that the PEC would perform all "mapping" of these new agents within 180 days of FDA approval. (CLOSED)

(8) Adderall®: This product is a Class II agent and cannot be "mapped" to another Class II agent because of Federal Regulations. The committee approved addition to the NMOP. (CLOSED)

(9) Coverage of agents specifically excluded by CHAMPUS: The following agents will not be provided by NMOP: lancets, OTC products (unless specifically included), drugs for cosmetic use (i.e., Renova®, Propecia®), devices, Clozaril®, smoking deterrents, injectable medications (unless specifically included), and vitamins (unless specifically included). (CLOSED)

(10) Same drugs, different manufacturers with different prices – NJ law prohibits substitution: These include Desogen®/OrthoCept®, TriPhasil®/Trilevlen®, Prinivil®/Zestril®, and Trandate®/Normodyne®. Capt Parrish requested, and received, the committee's approval to seek alternatives through MM to possibly move the filling of those prescriptions to another state where those items are interchangeable. (CLOSED)

(11) Birth control pills – 28-day packages are cheaper than 21-day packages: Capt Parrish will work with the DAPA section at DSCP to see if 21-day package price could be changed to matched the 28-day package price. (OPEN)

(12) Time limits for refills – SOW currently states that 75% must be used before refilling: Until recently, M-M had been filling all refill requests, regardless of time limit. M-M has been informed that they will follow 75% rule. Now, M-M returns refill requests to patients unfilled, if 75% rule is not met. The committee stated that the needs of the patients have to be considered and that undue hardship should not be placed on them. Mr. Lowe responded that the VA does not return early refill requests, that these are held until the established time limits are met, then the requests are filled and mailed to the patient. COL Strampel asked if this could also be done by M-M. Capt Parrish stated that this would require a modification in the SOW and could possibly cost the government more. Issue is tabled until next meeting by which time Capt Parrish will check to see if and how much a change in the SOW will cost. (OPEN)

o. Viagra® policy: Issues of concern are safety and cost. Since Health Affairs has already written a "draft" policy and it appears that it will be imminently approved, the committee will defer on this issue. (OPEN)

5. ADJOURNMENT: The meeting was held from 1400-1700 on 13 July 1998 and from 0800-1515 on 14 July 1998. The next meeting will be held on 13 November 1998. The office of record for official minutes is the Pharmacoeconomic Center, Fort Sam Houston, TX 78234.

ERROL L. MORAN
COL, MS
Co-chairman

WILLIAM D. STRAMPEL
COL, MC
Co-chairman